HEALTH EFFECTS IN COMMUNITY RESIDENTS NEAR A URANIUM PLANT AT FERNALD, OHIO, USA

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Abstract
Objectives: Health outcomes in persons who lived in the area surrounding a U.S. Department of Energy (DOE) uranium processing plant near Fernald, Ohio were evaluated using data of Fernald Medical Monitoring Program (FMMP) participants. **Methods:** Residential history information was used to identify participants who lived in close proximity to the plant (less than 2 miles), in the direction of groundwater runoff (south of the plant), or used a well or cistern as a drinking water source. Standardized prevalence ratios (SPRs) for certain disease endpoints were calculated using the U.S. National Health Interview Survey (NHIS) and the National Health and Nutrition Examination Survey (NHANES) data files for comparison rates. **Results:** Findings suggest that prior living within the Fernald exposure domain is related to increased prevalence of urinary system disease. Statistically significant elevations of bladder disease (standardized prevalence ratio or SPR = 1.32) and kidney disease (SPR = 2.15), including sub-categories, kidney stones (SPR = 3.98) and chronic nephritis (SPR = 2.03) were noted, as well as increased rates for hematuria and urethral stricture. In regression analyses with adjustment for age and sex, serum creatinine levels were increased in those who had lived close to the plant. Increased white blood cell count and hemoglobin levels, and decreased mean corpuscular volume were also found in those living less than 2 miles from the plant. Those who used a well or cistern for drinking water were found to have increased urinary microalbumin, red blood cell count and hematocrit. **Conclusions:** These preliminary findings will provide the basis for future hypothesis testing incorporating important determinants of exposure not included in this study, such as duration and calendar year of exposure, location relevant to prevailing wind direction, and age at exposure.

Key words:
Uranium, Environmental medicine, Surveillance, Prevalence, Cohort

INTRODUCTION

In 1951, the U.S. Department of Energy (DOE) constructed a uranium and thorium processing plant in Fernald, Ohio, known as the Feed Materials Production Center (FMPC). This industrial facility processed uranium ore, which was chemically converted into a series of uranium oxides and salts, primarily uranium trioxide and uranium tetrafluoride. Later the focus shifted to processing other types of other uranium feed materials, such as uranium concentrates and recycled materials from various stages of nuclear weapons production, sent to Fernald from other DOE sites.

The ore concentrates and recycled materials received at the site were dissolved in nitric acid to produce a slurry containing uranyl nitrate, later mixed with an organic solvent, tributyl phosphate dissolved in kerosene, for extraction out of the aqueous phase [1]. The purified uranyl nitrate was then re-extracted from the organic solvent into

deionized water and then thermally denitrated to produce uranium trioxide (UO_3 or orange oxide). Orange oxide was then converted to UF_4 or green salt by reduction with heated hydrogen followed by reaction with anhydrous hydrogen fluoride. Green salt was shipped to other sites for enrichment by gaseous diffusion, or used on-site to produce uranium metal by chemical reduction at very high temperatures. Metal was then machined or extruded into tubular form, and fabricated into reactor fuel cores and target elements that were shipped to other DOE sites in the nuclear weapons complex. From 1952 to 1980, the FMPC received approximately $3.62 \cdot 10^8$ kilograms (kg) (362 000 metric tons) of uranium and shipped approximately $3.58 \cdot 10^8$ (358 000 metric tons) to offsite locations [2]. Smaller amounts of thorium were processed intermittently during the 1950s and again from 1964–1980 [3].

Dusts and particulates, created at different points of the production process, were released into the atmosphere through dust collectors and scrubbers and dispersed by air currents [3]. Yearly uranium release estimates increased sharply from the initiation of production in 1951 to a peak of 61 309 kg in 1955, and then decreased gradually but remained above 10 000 kg per year until 1963 [4]. After 1964, release estimates remained below 5000 kg per year decreasing gradually until the end of production in 1989. During the years of plant operation (1951 through 1988) it has been estimated that 310 000 kg of airborne uranium dust were released into the atmosphere. Average annual concentration of uranium in the air at the perimeter of the FMPC from 1960 through 1963 was over 1000 times the natural background concentration of uranium, ranging from 70–346 fCi m^{-3} at four directional perimeter air-monitoring stations [4, Appendix N]. Air concentrations decreased with distance from the site but were greater to the east, the prevailing wind direction [4].

An additional 99 000 kg of uranium and associated radionuclides were also discharged into surface water in either solution or suspension of very small particulates [3]. Wastewater effluent was regularly discharged into the Great Miami River, east of the site, and periodically through storm sewers into Paddy's Run Creek, west of the site [3]. Uranium releases to the river peaked in 1961

(7300 kg) and to the creek in 1974 (1722 kg) [3, Appendix L]. Several uranium species of both the +4 and +6 oxidation states may have been present in solution in liquid waste streams during the production period. Releases of thorium and one of its decay products, ^{228}Ra, occurred when thorium was processed at the site in 1954–1957 and 1964–1988 [3]. Releases of ^{226}Ra, a decay product of ^{238}U, occurred throughout the history of the site. Radium isotopes, ^{226}Ra and ^{228}Ra, were the most important potential contributors to offsite radiation dose relative to the other radionuclides released to water [3]. Uranium contamination of ground water offsite was noted in 1981, when private wells were first sampled, and a further evaluation of the groundwater plumes underlying the FMPC at the end of 1988 also indicated contamination of offsite wells [5]. The principal source of uranium contamination in groundwater south of the site (known as the South Plume) appear to be the historical liquid effluent releases into Paddy's Run Creek either directly or via an on-site storm sewer outflow ditch. Data from monitoring wells and groundwater modeling defined the South Plume in 1989 as an elongated ellipse oriented in the north-south direction from the southern perimeter border of the site [3]. Groundwater models suggest that the uranium contamination did not reach offsite wells before 1968 and appear to have peaked in 1977–1978 [3].

Many residents of the area used cisterns as a source of drinking water, collecting rainwater from roof gutters, but there has been little sampling of water stored in these reservoirs. In an analysis of tap water at homes with cisterns, conducted in 1988, uranium concentrations were below 1.2 pCi L^{-1} [6]. For one cistern, disconnected from the roof gutters for two years prior to sampling, a dipper was used to collect water directly from the cistern. Uranium concentrations of two samples from this cistern were 20.3 and 29.3 pCi L^{-1}.

Although initial concern focused on releases of uranium, with further investigation it became evident that substantial amounts of radon and its decay products also were released from waste materials stored in large silos and metal drums at the site, and dispersed to the air surrounding the site [3]. The amount of radon (^{222}Rn) released from

the silos for 1959–1979 has been estimated at 6200 curies (Ci) each year, with a total 160 000 Ci released from all sources during the entire production period (1951–1988). In addition to radioactive contaminants, many other non-radiologic toxic substances were present in the production area as materials, by-products, or products, including chlorinated and non-chlorinated solvents, metals and metal salts, and nuisance dusts.

Community residents may have been exposed to both radiologic and non-radiologic contaminants through air dispersion of emissions from the plant, groundwater pathways, and soil contamination. Sponsored by the Centers for Disease Control and Prevention (CDC), the Fernald Dose Reconstruction Project provided a detailed characterization of historical radiation exposure [3] and developed an algorithm to estimate doses to persons who lived within the exposure assessment domain (an area within a 10 km radius of the perimeter of the plant property) [4,7]. Doses calculated for nine hypothetical residents with different exposure scenarios showed that inhalation was the most important mode of exposure and that radon decay products were the source of most of the dose. Transport models predicted that the deposition of radioactive materials would be greater to the east of the plant, in the prevailing wind direction [7].

Maximum levels of uranium concentration in the kidneys (i.e., for the highest year) were also estimated by this CDC dose reconstruction project. For one scenario, a male living within 2 km from the site who inhaled uranium particles and used well water as a drinking water source, the median estimate of maximum uranium concentration to the kidney was 0.75 μg g^{-1}, above the level that mild kidney effects could possibly occur (0.5 μg g^{-1}). This CDC project also estimated that the accidental short (1 hour) release of uranium hexafluoride in 1966 could have resulted in a kidney concentration of 0.85 μg g^{-1} in a person who inhaled the gas directly downwind of the site [4]. In a recently published draft Agency for Toxic Substances and Disease Registry (ATSDR) Fernald Public Health Assessment (FPHA), the agency concluded that past exposure to the chemical properties of uranium through ingestion of groundwater from privately owned wells in the South Plume posed a public health hazard to children and adults [8].

In January 1985, a class action lawsuit was filed by the citizens of the area against the U.S. DOE, resulting in a settlement of $ 75 000 000. A portion of these funds were designated for medical surveillance through the Fernald Resident Medical Monitoring Program (FMMP), which began examining patients in October 1990, and will continue for approximately 20 years.

The following is a report of a standardized prevalence ratio (SPR) study of chronic disease morbidity in persons who lived in the area around the Fernald plant, using the U.S. National Health Interview Study (NHIS) and the Third National Health and Nutrition Examination Survey (NHANES III) data files for comparison. The intent of this data analyses was to determine if an excess disease burden exists in this population, prior to designing other epidemiological studies using individual exposure estimates. This study did not include cancer outcomes, because they have been studied separately, nor reproductive or heritable effects, because they were beyond the scope of this effort.

MATERIALS AND METHODS

Subjects

The cohort for this study consisted of all persons enrolled in the FMMP who were 18 years of age or older at the time of the first examination (N = 8496). Eligibility for the FMMP required residence within a 5-mile radius of the FMPC for a minimum continuous 2-year period between January 1, 1952, and December 18, 1984. Former workers at the plant were excluded because their potential dose is representative of an occupational rather than an environmental exposure. Twenty-one FMMP participants who were receiving chemotherapy at the time of the first examination were also excluded from the analysis of laboratory data, which is consistent with NHANES exclusions, as well as seven who did not provide biospecimens, leaving 8464 subjects. Informed consent was obtained from FMMP participants at the time of each examination, including a statement permitting use of data for statistical analyses.

Data collection

Data collected at the time of the first FMMP medical examination were used for the analysis. Physicians obtained a medical history, including current and past medical problems, hospitalizations, surgical and medical procedures, and family medical history. The medical problem list was then assigned codes of the International Classification of Diseases, 9th revision (ICD-9) by certified medical record coders. Medical records from other institutions were used to clarify and verify some participants' diagnoses. A complete physical examination and laboratory testing of blood and urine was included in the standard protocol. Systolic blood pressure was recorded at Korotoff sound K2 and the diastolic pressure at K5 [9]. Personnel were also given specific instructions regarding cuff size; pediatric, large, and extra-large cuffs were available in addition to the standard size cuffs. Information on lifestyle risk factors, location of residences and drinking water sources, and other measures of exposure via various pathways was obtained by questionnaires mailed prior to the initial examination. A second source of information about medical conditions in FMMP participants was a set of four questions included in the questionnaire. Items were "Do you have heart problems (diabetes, cancer, chronic bronchitis or emphysema)?"; response categories were "yes," "no," and "not sure". At the examination visit the nurse reviewed the completed questionnaire and performed a brief check of data completeness and the participant's responses to critical questions.

Residence addresses were coded for location and entered into a computer data file, which was then used to produce a residential history report for each program participant. A copy of this report was sent back to the participant with the second yearly questionnaire, along with instructions for verifying the information and, when necessary, providing additional information to assign location codes. Approximately 45% of participants provided additional or corrected data. Residential history data were used to identify subsets of participants: those who lived close (less than 2 miles) to the facility, those who lived in the southern quadrant of the exposure domain (the direction of groundwater runoff from the facility), and those who used a well or cistern as a drinking water source. These categorical assignments served as crude exposure surrogates, since no quantitative estimates of exposure have been calculated for participants of the FMMP. Important determinants of exposure, such as duration of residence, calendar year of residence and location of residence relevant to the prevailing wind direction were not included in this initial analysis of the data.

The process of selecting the adverse health outcomes to be studied began with review of the scientific literature and historical records of the FMPC in order to develop a list of health effects associated with known potential exposures originating from the Fernald plant. Interviews were conducted with area medical practitioners, examining physicians of the FMMP, local and state health officials, and community residents to obtain information about perceived disease excess. Investigators then considered the list of potential health effects in conjunction with issues such as types of data available in comparison with data sets, discrepancy in methods of data collection, and statistical power considerations. Disease outcome categories selected *a priori* were: goiter, other thyroid disease, chronic bronchitis, asthma, emphysema, nephritis, other kidney disease, and diabetes mellitus.

Comparison databases

Sponsored by the U.S. National Center for Health Statistics (NCHS), NHANES III was designed to obtain nationally representative information on the health and nutritional status of the population of the United States. The sampling plan follows a complex, stratified, multi-stage, probability cluster design, resulting in a representative sample of the entire civilian, non-institutionalized population of the United States. The NHANES protocol included a home interview followed by a standardized examination in a mobile examination center, which traveled over the entire country. As part of the examination, blood and urine specimens were obtained from all participants, and analyzed by laboratories managed by the NCHS [9]. The interview included specific questions on presence of medical conditions such as goiter, diabetes, kidney and bladder disorders, and chronic bronchitis.

The NHIS is also conducted by the NCHS and elicits interview information on the health of the non-institutionalized civilian population of the United States [10,11]. Sampling and interviewing are conducted each year with a sampling plan that follows a multistage area probability design that permits the representative sampling of households throughout the U.S. Items on the medical condition lists used during NHIS interviews included goiter or other disorders of the thyroid, diabetes, kidney trouble, bladder disorders, high blood pressure (hypertension), and chronic bronchitis. Other questions asked about recent physician visits and hospitalizations. A three-year period of NHIS data (1991–1993), corresponding to the same time period of the FMMP first data collection, was used for the analyses. The use of data from 3 years created a larger data set with more stable rates than from one year only.

Health outcome data for both the NHANES and NHIS projects were obtained by trained interviewers, but questions about medical conditions had different time frames (Table 1). In the NHIS project, only one family member was interviewed about the health status of all family members. The information about each family member was then recorded separately. Following data collection, NHIS assigned medical conditions and corresponding ICD-9 codes to each study subject based on a review of all information obtained in the interview. The NHANES data files contained uncoded response data to the medical condition questions, to which we then assigned ICD-9 codes to create a file format similar to the FMMP and NHIS data.

Many components of the NHANES medical examination were also similar to the FMMP protocol. Measurements of blood pressure and results of laboratory tests of whole blood, blood serum and urine, reported in NHANES data files, were used in comparisons to FMMP examination findings.

Statistical analysis

Rate calculations

FMMP computer files containing coded medical diagnoses were searched for ICD-9 codes of the medical outcomes chosen for the study, and used to calculate age- (within 5 years) and sex-specific rates for each diagnosis. For the FMMP population, persons who were assigned more than one ICD-9 code within a condition category were counted as only one case for that condition category. Four FMMP questionnaire items on medical conditions were also used to calculate a separate set of rates for an additional comparison to NHIS and NHANES data. Although these questionnaire data were probably not as accurate as the physician history data, the method of questionnaire self-report was more similar to the NHIS and NHANES interviews, which were not conducted by physicians.

The NHIS and NHANES data files of health conditions [12–15] were imported into SAS, selecting only records for those 18 years or older and non-Hispanic whites (to be comparable to FMMP data), and used to calculate age- and sex-specific rates for each medical condition in these comparison populations. For both projects, sampling weights have been developed to account for the survey design and to provide an adjustment for survey non-response. The use of the correct sampling weights is required to provide unbiased national estimates, as well as to accurately access the sampling error of statistics based on the survey data. When the appropriate sampling weights are used, the data are representative of the total U.S. population [11]. The approach used for applying the sampling weights and determining the NHIS prevalence estimates was taken from documentation contained on the NHIS CD-ROM [12–14]. NHANES sampling weights were applied using similar documentation [15].

Table 1. Variations in data collection methods

	FMMP	NHIS	NHANES III
Method	Physician recorded medical history information	Interview conducted by trained interviewer	Interview conducted by trained interviewer
Questions		**During the past 12 months,** did anyone in the family have (condition)?	Has your doctor **ever** told you that you have (condition)?
		Who was that?	Do you **still have** (condition)?

The NHANES interview questions did not ask about renal disorders. Rate calculations for renal disorders in the FMMP group followed the NHIS method of recoding ICD-9 codes for assignment to condition categories [13,14]. NHIS grouped the renal disorder ICD-9 codes into three recode categories for kidney disorders and two recode categories for bladder disorders (bladder infections, other bladder disorders). Because nephritis was a condition selected for study *a priori*, a subset category was created for nephritis by selecting only those persons with ICD-9 codes of 582.0–583.9. In the NHIS recode method, certain renal conditions (such as renal failure) were not placed in any of the NHIS renal disorder recode categories, but were included in the NHIS "other" category. Other ICD-9 codes within the range of 580 to 599 (kidney and bladder disorders) were not used in any of the NHIS recode categories. We chose to place these conditions in "remaining kidney/bladder disorder" condition categories.

Standardized prevalence ratios

The standardized prevalence ratio (SPR) is calculated by the same method as used for calculation of the standardized mortality ratio (SMR), but using prevalent disease in an individual rather than cause of death as the endpoint. The SPR (number of observed prevalent cases/number of expected prevalent cases) was determined for each medical condition by comparing the number of prevalent cases in the FMMP study population to the calculated expected number, based on either NHIS or NHANES data. The NHANES or NHIS rates were applied to the numbers of FMMP participants in age- and sex-specific groups to determine expected numbers of cases for each group, which were then summed across all age groups. Confidence intervals were calculated for each SPR according to methods described by Breslow and Day [16]. For observed cases of 50 or less, exact confidence limits were obtained by first finding the lower (L) and upper (U) limits (μ_L and μ_U) for the mean of a Poisson-distributed observation, and then dividing these limits by the expected number of cases to yield the lower and upper limits for the SPR. Byar's approxima-

tion was used to calculate the confidence limits for SPRs when the observed number of cases was greater than 50 (17). The exact method and Byar's approximation agree very closely when the number of observed cases is greater than 50. Statistical significance was declared at the 0.01 alpha level, and was not adjusted for multiple comparisons, because a primary objective of the study was to provide direction for future analyses incorporating exposure modeling.

Analysis of blood pressure and laboratory test data

For blood pressure data in both the FMMP and NHANES files, SAS was programmed to iteratively select the second blood pressure taken, except when only one blood pressure reading was obtained. Univariate statistics were generated to evaluate laboratory data in both the FMMP and NHANES files. Means, medians, and standard deviations were calculated for each age- and sex-specific group, with upper age groups condensed into a "75 years and older" category. Additional preliminary analysis was conducted on the data, including generation of histograms, and normal plots and graphs of mean values by age and sex group. Wilcoxon rank-sum tests were conducted to compare median values (FMMP and NHANES) within each age and sex group, testing for significance at an alpha level of 0.05.

Laboratory test data were also examined in multivariate linear regression analyses. Tests for normality and homogeneity of variance were conducted on continuous variables, and values were appropriately transformed as necessary for linear regression analyses. Data for each continuous variable then served as the dependent variable in a linear regression model containing age, sex, and group (FMMP or NHANES) as independent variables. Some models also contained a variable for any history of using a well or cistern as a drinking water source. Parameter estimates, standard errors, and p-values were calculated for each of the cofactors. Additional analyses were performed using only the FMMP population, with exposure factors (distance, direction, and drinking from a well or cistern) in the model.

RESULTS

Population demographics

The FMMP (N = 8496) and NHANES (N = 7312) populations used in the analysis were of similar size, but the NHIS population (N = 34 202) was much larger. Age distribution for both FMMP females and males was similar to, but slightly younger than, the NHIS population. Upper age groups were oversampled in NHANES, creating a skewed age distribution. Median age for FMMP participants was 43 years; 99.5 % were white non-Hispanics. We selected data of only white non-Hispanics from the NHANES and NHIS files. Most FMMP participants (74.3%) had family incomes ≥$ 20 000 at the time of their first medical examination (in 1990 to 1993) and 84.4% had graduated from high school or achieved a higher level of education. Smoking history statistics were similar to other populations, with 22.6% current smokers and 25.5% former smokers. In the NHIS population used for this analysis, 26.3% reported they were current smokers and 25.3% former smokers; in the NHANES population, 23.3% were current smokers and 31.6% former smokers.

The subset of the FMMP population who lived within 2 miles of the plant had slightly more in the <$ 20 000 income category (29.2%), the <high school graduate category (19.9%), and the current smoker category (27.5%).

Residence location and drinking water source

On questionnaires, FMMP participants were asked to list the address of any residence within a 5-mile radius of the plant during the period from the first year of production (1952) to the date of the questionnaire completion. A substantial portion (N = 3507 or 41.3%) of the FMMP population lived at some time within 2 miles of the site. When the exposure domain was divided into four quadrants, only 29.6% (N = 2511) ever lived in the south quadrant, the primary area of groundwater runoff. The majority of FMMP participants (63.6%) stated they used a private well or cistern as their drinking water source while living in at least one residence within the exposure domain, with 28.1% drinking from a well at a residence within 2 miles of the site. Using the quadrant model, 20.2% had ever drunk from a well in the south quadrant.

The NHANES survey also contained a question about drinking water source: "What is the source of your home tap water?," with response options "private or public water company," "private or public well," "spring," or "don't know (DK)." In response to this question about current drinking water source, 18.7% of NHANES subjects indicated that their drinking water source was a private or public well.

Medical conditions

Statistically significant (p = 0.01) elevations in both kidney disease (SPR = 2.15; 99% CI = 1.86–2.48) and bladder disease (SPR = 1.32; 99% CI = 1.11–1.56) were present in the FMMP population (Table 2). Several categories contributed to this excess, including chronic nephritis (SPR = 2.03, not statistically significant), and the category of "other bladder disorders" (SPR = 8.09). For kidney stones, a condition with presumably high validity of self-reported data, the SPR was 3.98. However, the NHIS question asked if the condition was present "during the past 12 months," whereas FMMP medical history data may have counted acute incidents more than 12 months in the past, which could have resulted in an upward bias in the SPR. The excess in cases of kidney stones was present in all age- and sex-specific groups. Comparison of unadjusted rates for conditions in the "remaining bladder disorder" category suggests that the higher prevalence in the FMMP population of hematuria (0.37% vs NHIS 0.02%) and urinary stricture unspecified (0.21% vs NHIS 0.00%) contributed to most of the rate difference in this category.

We also examined the prevalence of disease in subgroups of the FMMP population defined by the exposure surrogates of proximity to the plant (<2 miles), source of drinking water (well or cistern), and direction from the plant. The SPR for kidney disease did not differ by distance or direction from the plant, or drinking water source. Drinking water from a well or cistern neither explained the differences in the SPR for kidney stones (SPR of 3.99 vs 3.96). The prevalence of bladder disease was somewhat

Table 2: Standardized prevalence ratios (SPR) of renal disorders in participants of the Fernald Medical Monitoring Program using NHIS (National Health Interview Survey, 1991–1993) data as comparison

Condition[1]	NHIS[2]
	SPR (99% CI)
Renal disease	
All kidney disease[3,4]	2.15* (1.86–2.48)
All bladder disease[5]	1.32* (1.11–1.56)
Kidney stones	3.98* (3.36–4.68)
Kidney infections	0.71 (0.46–1.06)
Other kidney trouble, NEC	1.11 (0.68–1.72)
Chronic nephritis[6]	2.03 (0.76–4.35)
Bladder infections	0.59** (0.40–0.84)
Other bladder disorders	0.17** (0.07–0.33)
"Remaining kidney disorders"[7]	1.96 (0.73–4.19)
"Remaining bladder disorders"[8]	8.09* (6.63–9.77)

[1] Patient asked during NHIS interview, "During the past 12 months, did anyone in the family have _____? Who was this?"

[2] Standard prevalence ratios and associated 99% confidence interval.

* Statistically significant excess at alpha = 0.01; ** Statistically significant deficit at alpha = 0.01; 99% confidence interval does not include 1.00.

[3] An FMMP participant having more than one diagnosis reported in an inclusive category such as "All kidney disease" and "All bladder disease" was counted only one time in the SPR analysis of that category.

[4] All kidney disease – ICD-9 codes 580–593.

[5] All bladder disease – ICD-9 codes 594–599.

[6] Chronic nephritis – subset of "Other kidney trouble", NEC, including ICD-9 codes 582 and 583.

[7] Remaining kidney disorders – ICD-9 codes within the range 580–593 not used in any of the NHIS recode categories.

[8] Remaining bladder disorders – ICD-9 codes within the range 594–599 not used in any of the NHIS record categories.

higher in the within 2-mile group (SPR of 1.51 vs 1.17), but was not different in those who lived south or east of the site or drank water from a well or cistern.

Thyroid disease

General population prevalence rates for goiter and "other thyroid disease" are generally quite low. Reported rates

from the NHIS and NHANES databases varied substantially with the different question formats. The NHANES disease rates obtained from the interview questions asking "ever had (condition)" produced higher condition rates and lower SPRs when compared to FMMP data (SPR = 0.59 for goiter and 0.66 for "other thyroid disease") (Table 3). However, when using NHIS and NHANES data generated from questions with a shorter time frame, such as the NHANES question "still have" and the NHIS question "during the past 12 months," comparison database rates were lower. Consequently, SPRs obtained with FMMP data comparisons were higher. The SPR for goiter obtained with data from NHANES "still have" question was 1.41; (99% CI = 1.01–1.91). Likewise, when using responses from the NHIS "during the past 12 months" question, both the SPR for goiter (2.50) and for "other thyroid disease" (1.48) were elevated. Age- and sex-specific rate comparisons demonstrated that FMMP goiter rates were higher than NHIS rates for all age groups from 20 through 79 years of age for females (with greatest discrepancies occurring in those aged 60 through 79), and from 35 through 69 years for males. A similar constant pattern was seen in age- and sex-specific rates for "other thyroid disease".

Proximity to the plant influenced prevalence of thyroid disease in the FMMP group. SPRs calculated using NHIS data were slightly higher for those living within 2 miles (SPR = 3.02 for goiter; SPR = 1.57 for "other thyroid disease") versus those who lived in the 3- to 5-mile area (SPR = 2.12 for goiter; SPR = 1.42 for "other thyroid disease"), but the SPRs for FMMP residents at ≥2 to 5 miles were still elevated at the 0.05 alpha level.

Diabetes mellitus

For diabetes mellitus, FMMP rates were similar to NHIS data (SPR = 1.09) (Table 3), but elevated when the analysis was restricted to those living within 2 miles (SPR = 1.32; 95% CI = 1.13–1.55). In contrast, when using the NHANES "ever" question data for comparison, the SPR was lower.

A mailed questionnaire sent to the FMMP participants prior to the first medical examination provided data that

Table 3. Standardized prevalence ratios (SPR) of thyroid and respiratory disorders and diabetes mellitus in participants of the Fernald Medical Monitoring Program using NHIS (National Health Interview Survey, 1991–1993) and NHANES III (Third National Health and Nutrition Examination Survey, 1988–1994) as comparisons

Condition	NHIS [1,2]	NHANES [1,3]	
		Ever	Still have
	SPR (99% CI)		
Thyroid diseases	1.55* (1.33, 1.79)	0.65** (0.56, 0.75)	
Goiter	2.50* (1.79–3.39)	0.59** (0.42–0.80)	1.41* (1.01–1.91)
Other thyroid disease	1.48* (1.26–1.73)	0.66** (0.56–0.77)	1.09 (0.93–1.28)
Diabetes mellitus[4]	1.09 (0.94–1.25)	0.80** (0.69–0.92)	
Respiratory diseases			
Asthma	0.85** (0.73–0.98)	0.45** (0.39–0.52)	0.70** (0.60–0.81)
Chronic bronchitis	0.19** (0.14–0.24)	0.17** (0.13–0.22)	0.31** (0.24–0.40)
Chronic bronchitis and emphysema	0.25** (0.20–0.32)	0.27** (0.22–0.32)	
Emphysema	0.61** (0.41–0.86)	0.52** (0.40–0.68)	

[1] Standard prevalence ratios and associated 99% confidence interval.

* Statistically significant excess at alpha = 0.01; ** Statistically significant deficit at alpha = 0.01; 99% confidence interval does not include 1.00.

[2] Patient asked during NHIS interview, "During the past 12 months, did anyone in the family have _____? Who was this?"

[3] Patient asked during NHANES interview, "Has your doctor ever told you that you have _____?" and "Do you still have _____?"

[4] NHANES interview did not ask "Do you still have ?" for diabetes mellitus and emphysema.

were collected with a method more similar to the questionnaire methods of the NHIS and NHANES. Questionnaire items asked about medical conditions, including diabetes mellitus and respiratory disease. SPRs calculated using responses to the item "Do you have diabetes?" produced SPRs that were similar to those calculated when the medical history data were used (1.00 with the NHIS comparison and 0.74 with NHANES).

Respiratory disease

The FMMP rates for respiratory disease, as noted in the physicians' medical history, were generally much lower than either NHANES or NHIS rates, especially for chronic bronchitis (Table 3). SPRs for asthma, chronic

bronchitis, and emphysema all represent statistically significant deficits, even when compared to the "still have" NHANES data. There were no differences when stratifying by distance or direction from the plant, except for emphysema, where the NHIS SPR for the within 2 miles subpopulation was relatively higher (SPR = 0.80 versus 0.49), although this probably reflects the higher smoking rates in this group. FMMP participants self-reported these respiratory conditions on questionnaires more frequently than they were recorded in the physician-obtained medical history. SPRs calculated using FMMP questionnaire data were higher (0.79 with NHIS comparison and 0.57 with NHANES), but still showed a statistically significant deficit of reported disease in the FMMP population.

Blood pressure

For most age- and sex-specific groups, both FMMP systolic and diastolic mean blood pressures were higher than those found in the NHANES examinations. In regression analyses using log transformed systolic or diastolic blood pressure as the dependent variable and adjusting for age and sex, both systolic (9.7 mm Hg) and diastolic (9.1 mm Hg) blood pressure were higher in the FMMP group, probably due to method bias. When analyses were conducted on the FMMP group alone, neither distance nor direction from the site influenced either blood pressure measure. Interestingly, using a well or cistern water source was related to a small but protective difference in systolic blood pressure, both for the combined NHANES and FMMP populations (-1.13 mm Hg) and the FMMP population alone (well or cistern use, -1.09 mm Hg).

Laboratory diagnostic tests (serum chemistry, hematology, and urinalysis)

When laboratory test data of the FMMP and NHANES populations were compared within age- and sex-specific groups using the Wilcoxon rank-sum test, almost all measures showed small, consistent differences between the two groups, most likely due to laboratory method differences. In many instances these minimal differences were statistically significant because of the large population size. Because there were no simple and reliable means to standardize for laboratory method biases, we have chosen to report only analyses restricted to the FMMP population where the same laboratory did all of the tests. Linear regression models were used to examine the effect of living less than 2 miles from the FMPC, within the south quadrant of the FMMP exposure domain, and using a well or cistern as a water source. Age and sex were retained as covariates in all models. We also performed similar analyses restricted to the NHANES population to assess the effect of using a well for drinking water.

Several small differences in serum chemistry and whole blood components were found within the FMMP population (Table 4). Although none would be clinically significant, small differences in study population statistics are sometimes the mark of an exposure effect on a population.

Small but statistically significant increases in serum creatinine, white blood cell (WBC) count, and hemoglobin, and decrease in mean corpuscular volume (MCV) were found among those in the FMMP population who lived less than 2 miles from the plant. For WBC, which had the largest proportionate increase, the adjusted subgroup mean for the less than 2 mile subpopulation was $6.39 \cdot 10^3/mm^3$ versus $6.12 \cdot 10^3/mm^3$ for those that lived ≥ 2 to 5 miles from the plant.

In the subpopulation that ever used a well or cistern while living in the FMMP exposure domain, alanine aminotransferase (ALT), red blood cell (RBC) count, hematocrit, and WBC count were higher than in those who only ever used municipal drinking water. When WBC count was tested in an additional regression model with both exposure variables (as well as age and sex), both distance from the plant ($p < 0.0001$) and using a well or cistern ($p = 0.0222$) were found to be associated with a statistically significant increase. This well/cistern group also had lower levels of urinary creatinine and higher levels of urinary microalbumin (Table 4). Levels of serum creatinine did not differ with drinking water source. The interaction term "age*well/cistern" was very significant for microalbumin, indicating that the increases in microalbumin level were larger for the older age groups. In contrast, a decrease in hemoglobin was the only alteration noted in well-water drinkers in the NHANES population.

DISCUSSION

This study provided an opportunity to screen for adverse health effects of low-level, chronic exposure to uranium and ionizing radiation, as well as of mixed chemical and other metal exposures from the FMPC. The number of potential subjects, the expansive database on those currently enrolled in the FMMP, the quality of the diagnosis and biologic testing data, and the ability to create exposure groups within the FMMP population enabled this research project to yield substantial information at a relatively low cost. SPR calculations identified medical diagnoses that warrant further study. The primary limitation was that exposure categorization of the FMMP population was

Table 4. FMMP subjects[1]: effect of residence within two miles or drinking water source on laboratory test results

Laboratory test [2]	Exposure terms			
	Variable[3]	Parameter estimate[4]	P value	Difference[5]
Alanine Aminotransferase	Well/Cistern	0.0291	P < 0.01	+0.55 U/L
Red blood cell count	Well/Cistern	0.0071	P < 0.001	$+0.03 \cdot 10^6/mm^3$
White blood cell count	Residence w/in 2 mi	0.0435	P < 0.001	$+0.27 \cdot 10^3/mm^3$
White blood cell count	Well/Cistern	0.0194	P < 0.01	$+0.12 \cdot 10^3/mm^3$
Hemoglobin	Residence w/in 2 mi	0.0016	P = 0.02	+0.06 gm/dL
Hematocrit	Well/Cistern	0.0080	P < 0.001	+0.34%
MCV[6]	Residence w/in 2 mi	-0.0029	0 < 0.01	-0.26 fL
Serum creatinine	Residence w/in 2 mi	0.0078	P = 0.02	0.01 mg/dL
Urinary creatinine	Well/Cistern	-0.0539	P <0.001	-5.42 mg/dL
Urinary microalbumin	Well/Cistern	0.0692	P< 0.01	+0.05 mg/dL
Urinary microalbumin	Age* Well/Cistern	0.0066	P < 0.001	–

[1] FMMP – Fernald Medical Monitoring Program, 1991–1994, data from first medical examination (N = 8464).
[2] Natural log of the laboratory test value was used in the analysis.
[3] FMMP participants categorized as ever drinking from a well or cistern or ever living within two miles of the FMPC.
[4] All models for regression analyses included age at time of test (years), sex and the exposure term as independent variables and the log transformed laboratory test value as the dependent variable.
[5] Estimated difference in laboratory mean values (geometric mean of the exposed-unexposed subjects) at mean levels of other variables included in the regression model.
[6] Mean corpuscular volume = (hematocrit • 10)/RBC count.

crude, with assignment based on a history of having "ever lived" within 2 miles or "ever used" a well or cistern in the exposure domain as a drinking water source. Important determinants such as duration and calendar year of exposure, location relevant to prevailing wind direction, and age at exposure were not captured by this crude method. Participants in the FMMP are a self-selected volunteer population, and therefore not necessarily representative of the entire cohort that ever lived within the FMMP exposure domain. Analysis of the demographic and lifestyle risk factor levels of this population, however, has provided some reassurance that the level of wellness in this population is at least similar, and perhaps "healthier" than the general population. Indicators such as higher educational

level and income, a large portion currently married (73%) at the time of the first medical examination, as well as low standardized mortality ratios for all causes (0.71) and cardiovascular disease (0.72) during the first several years of follow-up, counter the notion that ill persons of lower socioeconomic groups may have been disproportionately represented in those coming for the free medical examinations. The rate of current smoking (23%) is almost identical to the behavioral risk factor surveillance system (BRFSS) rate for the southwest Ohio region (24%) for the same time period [18]. It is also unlikely that persons living within the Fernald exposure domain would link conditions, such as renal system disease with potential exposure from the plant, because media reports at the time of the

first examinations did not mention renal disease as a potential health effect.

Different methods of interview data collection introduced complexity into interpretation of SPR findings. FMMP data used in calculation of SPRs for the selected medical conditions came from a physician-recorded medical history obtained at the first medical examination, with each physician using his/her usual approach to taking history. These diagnoses, recorded on the subject's medical history form, were used to calculate age- and sex-specific prevalence rates for the FMMP population. In contrast, data for prevalence rates for the NHIS and NHANES populations came from responses to a standardized set of questions for each project, administered by a trained interviewer. Furthermore, the time frames of questions asked by these two surveys were different. The NHANES "has a physician ever told you" question covers the longest time span; "yes" responses to these questions represent true lifetime period prevalence. In contrast, "yes" responses to the NHANES "still have" question represent point prevalence, which should translate into lower rates. For the NHIS question covering the immediate previous 12-month period, the rate of "yes" responses should be similar to the NHANES "still have" question. Differences in the time frames of questions are an important factor in interpreting rate differences for more acute conditions such as kidney stones, but should be less influential on rates generated from questions about chronic conditions, such as diabetes mellitus, chronic nephritis or thyroid disease.

The FMMP medical history data may not represent true period prevalence, because physicians may not have always recorded chronic illness, such as bronchitis, where an exacerbation of symptoms was not present at the time when the medical history was taken. It is also likely that certain easily recognized conditions anticipated to recur in the future (such as kidney stones) probably were more likely to be recorded than conditions that were not as distinct. However, these response biases also may have been present in the NHIS and NHANES interviews.

Differences in FMMP and NHIS coding protocols may have influenced the SPRs for kidney and bladder conditions although the elevated SPRs for the overall categories of kidney and bladder diseases are impressive. Research that continues to explore the extent of renal disease in this Fernald area population is critical. The study investigators are proceeding with further analyses of red blood cell and hematocrit levels, and microscopic hematuria, and plan to examine the relationship of these parameters to both kidney disease and uranium exposure. The first FMMP medical examination also included measurement of urinary beta-2-microglobulin, which will provide an opportunity to study this marker of metal toxicity in a large uranium exposed population.

The excesses in nonmalignant kidney and bladder disease found in this study are consistent with the recent finding of excess renal cancer incidence in the FMMP over a seven-year period of follow-up (standardized incidence ratio or SIR = 1.95; 95% CI = 1.09–3.21; 15 cases observed), similar to the four year follow-up findings, reported earlier by Pinney and Wones [19]. Earlier analyses had also detected a strong association with the joint effect of living close to the plant and using a well as the water source [20], with the risk curve decreasing to 1.0 (or no excess risk) at approximately 2.0 miles from the perimeter of the site. In all analyses, findings of exposure effect were limited to the group that resided within 2 miles of the site perimeter.

Animal studies have demonstrated potent nephrotoxicity of uranium, primarily to the proximal tubules, although human studies of chronic occupational exposures have not been consistent in documenting clinical abnormalities in renal function [21]. Inhalation of uranium particles is the most common route of occupational exposure. Uptake can occur by ingestion, but the human gastrointestinal tract probably only absorbs 1–2% of the soluble uranium present [22]. Uranium absorbed into the blood after either inhalation or ingestion is principally passed through the kidney, selectively accumulated in the proximal tubule with a biological half-life of approximately one week for 95% of the renal deposits [23].

Studies of uranium-exposed populations have reported excess in urinary system disease in workers at DOE facilities, international facilities, and uranium miners. Dupree-Ellis et al. [24] found an elevated SMR of 1.88 for chronic nephritis in workers employed at the Mallinckrodt uranium

processing plant, a facility with processing operations very similar to Fernald. SMRs for kidney and bladder cancer were not elevated, although in the highest radiation dose group (160 mSv) there were 4 kidney cancer deaths observed and 1.2 expected. Polednak et al. [25] investigated mortality among 8345 workers exposed to uranium at a processing-plant at Oak Ridge, Tennessee. The standardized mortality ratios for diseases of the genitourinary system were elevated. In another mortality study of a large cohort employed at a uranium enrichment plant in the UK, McGeoghegan and Binks [26] reported an SMR of 182 for chronic renal failure and an association between incidence of bladder cancer and cumulative radiation exposure lagged by 20 years. They did not find any excess in renal cancer mortality in the cohort of radiation workers. In a combined cohort of female workers from 12 DOE sites, Wilkinson [27] found a statistically significant excess in deaths from "other genitourinary system diseases," excluding cancers (115 observed and 89.23 expected, SMR = 1.29). In the sub-cohort of Fernald workers, the SMR for urinary cancers was 2.28, although only 2 cases were observed. Previous studies of uranium miners [28] and uranium millers [29] have noted increased mortality due to chronic and unspecified nephritis and renal sclerosis. It is reasonable to expect that worker exposures would have been many times higher than exposures to Fernald area residents. A workplace hazard evaluation conducted by the National Institute of Occupational Safety and Health (NIOSH) showed significantly increased beta-2-microglobulin urinary excretion (a biomarker of uranium exposure) compared to controls in workers exposed to uranium dust, but there was no evidence of reduced renal function [30]. However, these mild effects may have been the result of a combination of the effects of the current uranium burden of the kidney, persisting renal damage caused by previous high acute exposures, and/or cumulative effects of uranium over a number of years [23].

Depleted uranium-exposed Gulf War veterans with retained metal fragments have excreted elevated levels of uranium in their urine during seven years after first exposure, but have not shown alterations in urinary function parameters (serum creatinine, beta-2-microglobulin, retinal-binding protein, urine creatinine and urine protein) between low and high depleted uranium-exposed veteran groups. The higher uranium-exposed group did have a higher percentage of eosinophils in their complete blood count. Exposures were estimated to be lower than in most occupational groups [31,32]. Other recent studies of the effect of elevated levels of uranium found naturally in some groundwater supplies have suggested that long-term ingestion may produce interference with proximal tubule function. In an environmental study of a Canadian population exposed to elevated levels of uranium in drinking water, Moss et al. [33] found kidney related bioeffects. Another study conducted by Mao et al. [34] of a population in Saskatchewan, Canada, investigated the association between drinking water levels of uranium and silicon and microalbuminuria. This study found a statistically significant positive association between increasing but normal levels of urinary albumin and the uranium cumulative exposure index, whereas no such association was noted with silicon exposure. A recent study conducted by Zamora et al. [35] of two communities from Nova Scotia and Ottawa, Ontario, Canada, reported that the chronic ingestion of uranium in drinking water affected kidney function (as manifested by glucosuria and the increased urinary excretion of the protein beta-2 microglobulin and the enzyme alkaline phosphatase), and the effects were mainly due to the action of uranium on the proximal renal tubule.

Emissions from the Fernald plant provided opportunity for both inhalation and ingestion of uranium. The oxide of uranium produced at the FMPC (UO_3) is generally regarded to be insoluble, as is green salt (UF_4) which also was produced in large quantities [21], although these compounds would have been more bioavailable when inhaled as a hot gases emitted from the plant stacks. Copious amounts of uranyl nitrate (UO_2NO_3), known to be quite soluble, were produced as a liquid by-product of the chemical separation process at the plant and were known to have spilled into the ground at the site. The episodic release of uranium hexafluoride in 1966 could have contributed to the kidney concentration in community residents who were directly downwind during the accident [4]. However, in a risk assessment of kidney cancer morbidity in community

residents of the 10-km Fernald exposure domain, the CDC estimated that there was only a *1% increase in lifetime risk due to exposure to site-related radioactive material* [36], but additional risk originating from the chemical toxicity of uranium was not included in the modeling.

The apparent excess in thyroid disease in the FMMP population is puzzling and could represent actual increase in disease prevalence, or could be due to biases created by different research methods. Additional study of the differences in population rates obtained by physician history-taking contrasted to in-person interview would be helpful in interpreting the findings of this study, as well as of other similar studies using NCHS databases. Regional differences in thyroid disease are known to exist, but initial analyses of disease rates from the Midwest subpopulations in NHIS and NHANES in comparison to FMMP thyroid disease rates produced SPRs similar to those obtained using the complete NHIS and NHANES populations. The excess in thyroid disease also could represent a self-selection bias. It is unfortunate that NHANES data for serum thyroxin were not available, because an analysis of this biomeasure could provide an estimate of the prevalence of sub-clinical disease, which is not subject to self-selection bias. ^{131}Iodine, linked to thyroid dysfunction in many research studies, was not known to be present at the FMPC. None of the known contaminants at the FMPC have been linked to health effects of the thyroid. Thyroid disease was chosen as an outcome for this study because several community physicians mentioned that there seemed to be an excess of thyroid disease in Fernald community residents.

Findings from this study should provide direction for public health initiatives for the Fernald area community and strengthen the ATSDR recommendations that two follow-up actions be considered: further evaluation of health outcomes among participants in the FMMP, and provision of additional health education activities, including educational workshops for health care providers in the Cincinnati area and Fernald community [5]. The results of this preliminary analysis also may provide guidance to local, state, and federal policy makers in allocation of resources for additional health risk assessment and environmental clean-up.

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