

Epidemiologic Studies to Evaluate Health Effects of Uranium Milling

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Cooperative Agreement U60 CCU 614568
August 12, 2002

The overall goals of this research effort are to test whether chronic respiratory and renal effects are associated with exposures to silica and uranium dusts in former uranium mill workers. These objectives are congruent with the directives of the United States Congress provided in Public Law 103-139 for a "study of the health effects of uranium milling, including the effects of exposure to radon, chemicals and uranium, on the health of those individuals employed in uranium mills in the southwestern United States during the period beginning on January 1, 1947 and ending on December 31, 1971."

The current health status of former uranium mill workers was investigated using a cross-sectional design. Employment records of uranium mill companies were used to establish a sampling frame for the recruitment of a sample of persons who worked in mills for at least one year in job titles associated with uranium processing, and who worked less than three months in underground uranium mines. Reference subjects of comparable ages and ethnic backgrounds who never worked in uranium mills (and less than three months in mines) were recruited from a pool of mend referrals provided by the former uranium mill workers. Clinical tests and interviews were conducted in a mobile testing van during August 1999 through March 2000, in Grand Junction, Colorado, Moab, Utah, and Grants and Albuquerque, New Mexico. Testing was conducted in a mobile van equipped to perform chest x-rays, spirometry, phlebotomy, and urine collection. Detailed work histories and health information were collected in standardized interviews with each subject. A total of 256 former uranium mill workers and 39 reference subjects were tested and interviewed. The research protocol and data collection instruments were reviewed and approved by the institutional review boards of NIOSH, the University of New Mexico Health Sciences Center, and the Navajo Nation. Informed consent was obtained from each research subject prior to clinical testing and interview.

Following data collection, clinical and laboratory chemistry analyses were conducted. Chest x-rays have been read independently by three NIOSH-certified B-readers, who followed International Labor Office guidelines to score the posterior-anterior films for the presence of opacities and profusion. Similarly spirometry tracings of the forced expiratory flow maneuvers were analyzed in accordance with American Thoracic Society guidelines, to obtain measures of forced vital capacity (FVC), forced expiratory flow (FEV1), and forced expiratory flow (FEF25-75). Analyses of urine samples quantified levels of beta-2-microglobulin, hexosaminidase, amino acids, and creatinine.

With assistance from epidemiologists and biostatisticians at NIOSH, the data have been assembled to begin statistical analyses of hypotheses to determine if respiratory and renal functions are impaired.

These hypotheses are:

The prevalence of cough, phlegm, wheeze, and dyspnea, corrected for cigarette smoking, are higher in former uranium mill workers than in the no mill employment reference group.

The prevalence of pneumoconiosis (profusion 1/0 or greater on chest x-ray films) is higher in former uranium mill workers than in the no mill employment reference group.

The mean percent predicted FEV1, FVC, and FEV1/FVC ratio are lower in former uranium mill workers than in the no mill employment reference group.

Mean levels of beta-2-microglobulin, hexosaminidase, and amino acids in urine are higher in former uranium mill workers than in the no mill employment reference group.

More specific estimates of potential exposure to silica dust and uranium will be derived. Work history data collected during the interviews will be used to calculate the total number of years of employment in uranium mills, and the number of years in specific job titles and process areas. These exposure metrics will allow consideration of the relationship of respiratory and renal status measures, and years of work in specific job titles (and areas) where exposure to silica dust and uranium were possible. Thus, our hypotheses can be restated as:

The percent predicted FEV1, FVC, and FEV1/FVC are inversely related to the cumulative number of years spent in crushing and sampling operations.

Levels of beta-2-microglobulin, hexosaminidase, and amino acids in urine are inversely related to the cumulative number of years spent in yellow cake drying and packaging operations.

In a previous study (Dawson, Madsen and Spykerman 1997), former uranium mill workers have voiced serious concerns about a broader range of health problems and impacts on quality of life). To investigate the potential impact of uranium mill employment on health-related quality of life, the following hypotheses will be tested:

The mean scores for quality-of-life batteries are lower in the sample of former uranium mill workers relative to the sample of reference subjects.

Quality-of-life measures are correlated with reduced spirometric lung function.

Quality-of-life measures are correlated with reduced renal function as reflected in urinary biomarkers.

Quality-of-life indices decrease with increasing number of years of work in uranium mills.

Specific Activities Completed Through the Cooperative Agreement

Selection and Recruitment of Former Uranium Millers

Lists of names and employment histories for former uranium mill employees were obtained from companies who either operated uranium mills or acquired ownership of the mining/milling holdings of those companies. Personnel records of four companies were reviewed and copied to microfilm. The records of a fifth company were obtained but not used because the work force was primarily comprised of individuals who worked after the 1971 period of interest, and because this facility was located away from the Four Corners area where most of the clinical testing was performed.

Records in these sources were screened to select those individuals whose employment in uranium mills

lasted for at least one year, and who appeared to have worked no more than three months in underground uranium mines.

Subjects were also recruited from a NIOSH database assembled by Richard Waxweiler in the early 1980s. These records were originally used to support a mortality study of workers from uranium mills in Colorado and southern Wyoming. Vital status of this cohort was ascertained by matching to Social Security Administration death tapes, and a list of living members was made available to UNM for recruitment.

Current addresses of former workers were located by record linkage with a database maintained by the U.S. Internal Revenue Service. Subsequently, names and social security numbers were submitted TransUnion, and in turn to the U.S. Postal Service. Phone numbers were obtained through Internet searches and published phone directories. If phone information could still not be found, requests were made to phone company directory assistance. Record linkage to the New Mexico Motor Vehicle Department provided address information for residents of New Mexico. Records of the Office of Navajo Uranium Workers were also reviewed to obtain contact information on former workers known to live on the Navajo Reservation.

Selected former workers were sent a letter via first class post that described the study. Potential subjects were asked to return a form in a pre-addressed postage-paid envelope, or to call UNM, to signal their interest in participation. If no reply was received within ten days, a second letter was sent and attempts began to reach the workers by telephone. Research staff telephoned all potential subjects who indicated interest and called non-responding individuals if a telephone number was known. Up to seven attempts to call subjects were made during various day and evening hours, and during weekdays and weekends. Telephone interviews were conducted to determine eligibility (at least 1 year in uranium mills, and no more than 3 months in underground uranium mines), and to arrange appointments for testing. During the screening interview, individuals were asked questions about the time worked in uranium mills and underground mines, job titles, age, ethnic background, tobacco use, and length of residence at current location. Some individuals came to the field sites without first returning letters or speaking with research staff by phone. The potential eligibility of these subjects was confirmed on our eligibility lists, and the *Screening Interview* was administered, before any decision to include the subject for testing.

Reference subjects were obtained from a pool of friends and acquaintances given to the investigators by mill workers who were enrolled in the protocol. Each mill worker subject was asked to provide the name of a friend of the same age and gender, who lived in the area but did not work in the uranium mills or mines. The referrals were contacted by telephone and the *Screening Interview* was administered in a manner identical to the process followed for the mill workers.

Testing at Community Sites

Clinical tests and interviews were conducted from August 1999 to March 2000 at sites in New Mexico, Colorado, and Utah (Table 1). Most tests were performed in a trailer van equipped to provide chest radiographs and pulmonary function tests (Miners' Colfax Medical Center Outreach Program, Raton, NM). At each field site, the van was parked alongside an office building or community center where rooms were available to conduct interviews in private areas. Eleven subjects received their clinical tests at the University of New Mexico Health Sciences Center.

Table 1. Clinical Test Dates and Locations

DATE	LOCATION
August 1999	Grants, NM
August to September 1999	Grand Junction, CO
September 1999	Moab, UT
November 1999	Shiprock, NM
January to March 2000	Albuquerque, NM

Interviews

Trained interviewers administered questionnaires during face-to-face interviews with the study participants. Prior to their scheduled interviews, subjects were mailed worksheet to document the sequence and dates of jobs held, and places of residence. These worksheets were mailed in advance and were intended to help the subject recall and organize employment and residence information. Ninety-one percent of the interviews were conducted in English. Nine percent of interviews were conducted in Navajo by trained native speakers experienced in administering interviews for research purposes.

Approximately one-half of the subjects received clinical tests and interviews on the same day. However, due to logistical constraints, interviews for the other half of the sample were conducted on days separate from the clinical testing. Usually the interviews were conducted at the site where the medical van was parked, but 25 interviews were conducted at the subject's homes and public places (library, classrooms).

The time required for each subject's clinical tests averaged 30 minutes. Interviews of former mill workers generally required 2 hours. Interviews of reference subjects required approximately 1 hour because a detailed record of mill jobs was not collected.

During the interviews, health history and quality-of-life information was collected before work history information to maintain the objectivity of respondents and to mask exposure status to the interviewers. The respiratory health questions in the *Health History Questionnaire* were based on the standardized and validated battery of questions developed by the American Thoracic Society (Ferris 1978). Additional questions were asked to characterize general health, renal disease, and musculoskeletal injuries. The *Quality of Life Questionnaire* assessed the performance of basic physical activities of daily life, performance of social roles, emotional state, intellectual functioning, and general satisfaction and perceived well-being. The questions contained in the *Quality of Life Questionnaire* were assembled from three standardized and validated instruments: the SF-12 (Ware and Sherbourne 1992; Ware, Kosinski, and Keller 1996), the National Health Survey Activities Questionnaire, and the St. George's Respiratory Questionnaire (Testa and Simonson 1996).

Information on work in uranium mills was obtained during the second half of the interview session. The *Work and Residence History Questionnaire* also assessed current employment status, work in occupations where exposure to respiratory hazards and renal toxins could occur, and places of residence. Detailed information on work in uranium mills was collected for each job title held, including job title, usual duties, area, use of personal protective equipment, and perceptions of dust, fumes, and radiation

levels in the areas worked.

Clinical Tests

Radiography: A single posterior-anterior chest x-ray was obtained using standard radiographic techniques. To optimize the evaluation of the film for the pneumoconioses, the film was exposed using guidelines recommended by the International Labor Organization (ILO 1980). Each film was interpreted according to ILO standards (ILO 1980, Merchant and Schwartz 1992) by two pulmonologists certified by NIOSH as B-readers. Patterns of opacity (profusions) were ranked along a 12-level scale. If the interpretation of the two readers differs by more than one level, films another interpretation was sought by a third B-reader. In situations of disagreement by one level of perfusion, the higher reading was used for data analysis. Radiographic pneumonconiosis was defined as a profusion of 1/0 or greater.

Spirometry: Pulmonary function tests were performed with a computerized spirometry system that met the performance recommendations of the American Thoracic Society (ATS 1995). Forced expiratory flow maneuvers were performed in the seated position with a nose clip. Quality control software provided standardized coaching instructions to the subjects during the performance of the maneuvers. Real-time displays of flow-volume and volume-time curves were available, and upon completion of each maneuver, a display was provided of all of the flow-volume curves, the FVC, FEV1, PEF, and expiratory time (minimum 6 s). All technicians performing spirometry completed a NIOSH-certified course in spirometry and were trained to use system software to make judgments of acceptability and reproducibility according to criteria recommended by the ATS (1995). A minimum of three maneuvers and maximum of eight were performed on each subject. For Navajo-speaking subjects, an interpreter provided instructions and coaching.

Following ATS interpretative guidelines (1991), obstructive disease is defined as the ratio of FEV1/FVC below the lower limits of normal based upon the predictive equations of Hankinson, Odencrantz and Fedan (1999). The presence of restriction from spirometric measurements will be inferred when the forced vital capacity is less than the lower limit of normal (LLN) for the predicted value from the Hankinson formulas and when the ratio of the forced expiratory volume in one-second to the forced vital capacity (FEV1/FVC) is greater than the LLN for that value (ATS 1991). Predictive equations specific to ethnic groups will be used for non-Hispanic whites and Hispanic whites (Hankinson, Odencrantz and Fedan 1999) and Native Americans (Crapo et al. 1988).

Analysis of Urine and Blood: Samples of urine and venous blood were collected at the Mobile Testing Facility. Upon arrival for clinical testing, subjects were instructed to void their bladders and were given at least one large cup of water to drink (750 ml). Subjects will be provided with a sterile container for clean catch of urine and instructions on its use. The aliquots of the 100 ml spot urine sample were transferred without additives into three 2 ml cryovials and three 5 ml cryovials. The pH of the remaining sample was then determined with test stripes, and if necessary, was adjusted to 6 or higher with 1.0 M NaOH, and aliquots of buffered urine transferred to three 2 ml cryovials. All aliquots were initially frozen at -20°C , and transported on dry ice to the laboratory, and then transferred to -80°C freezers for storage until analysis.

Venous blood samples were obtained from antecubital sites. Samples were drawn into three 5 ml evacuated tubes without anticoagulant, allowed to clot, and centrifuged at 1200g for 10 minutes. Serum

was drawn off and transferred to cryovials and initially frozen at -20°C , transported on dry ice to the laboratory, and transferred to -80°C freezers for storage until analysis.

Creatinine concentrations in urine and serum were determined enzymatically using a Kodak Ektachem DTC60 fluorometric analyzer. Serum samples were analyzed without dilution while the urine samples were diluted 20-fold with distilled water prior to analysis.

Amino acids were quantified in urine samples using reversed-phase high performance liquid chromatography (HPLC) (VanderJagt et al. 1997). Urine samples were deproteinated by 10K sieve filtration. A 20 μl aliquot of the filtered sample was transferred to a 6 x 50-mm glass tube, dried in a vacuum, and then treated with the derivitizing agent phenylisothiocyanate (PITC) under alkaline conditions to yield phenylthiocaramoyl amino acids. After derivitization and evaporation, the sample was dissolved in 0.1 ml buffer A (0.07 M sodium acetate, pH 6.5, containing acetonitrile 2.5% by volume and 1 ppm EDTA, Ca^{2+} salt). The derivatized amino acids were then separated by HPLC using an Ultra WISP 715 autoinjector and a Water Pico Tag solvent delivery system (Model 510). Samples were eluted using a gradient consisting of buffer A and B (acetonitrile:water:methanol, 45:40:15 by volume) over 64 minutes at flow rate of 1 ml/min. The column effluent was monitored at 254 nm and the signal integrated using Maxima 850 software. A recovery of between 97 and 107 percent was determined by the addition of known amounts of amino acids to urine specimens.

β -2-microglobulin (β -2-M) levels in urine were determined by chemiluminescent immunometric assay (Babson 1991) using the Immulite Beta-2 Microglobulin system. A polystyrene bead enclosed within a individual test units are coated with a polyclonal antibody specific for β -2-M. Undiluted urine and alkaline phosphatase-conjugated monoclonal antibody were incubated for 30 min at 37°C within test units with intermittent agitation, and β -2-M in the sample was bound to form an antibody sandwich complex. Unbound conjugate was then removed by centrifugal wash, after which chemiluminescent substrate was added and the test unit was incubated for an additional 10 minutes. The substrate, a phosphate ester of adamantyl dioxetane, undergoes hydrolysis in the presence of alkaline phosphatase to yield an unstable intermediate which emits light in proportion to the amount of β -2-M that is measured by the luminometer.

Total hexosaminidase activity in urine was determined by fluorometric assay. The substrate used was 10 mM 4-methylumbelliferyl-N-acetyl-B-D-glucosamide dissolved in 0.1 molar citrate-phosphate buffer (pH 4.4). The samples were thawed and 20 μl of substrate solution was added to the assay tubes containing 80 μl of substrate "master mix". The samples were then incubated at 37°C for 30 minutes in a shaking water bath. To end the reaction 2.0 ml of "kill buffer" (0.05 M glycine / 0.2M ammonia hydroxide adjusted to pH 10.5) was added. Fluorescence was measured at a wavelength of 365 nm. The extent of substrate cleavage was determined by comparison of fluorescence of samples against a standard curve prepared with 4-methylumbelliferone dissolved in glycine-ammonia hydroxide buffer. Blanks and standards were included in each assay run.

Exposure Assessment

Total number of years worked in uranium mills and in specific jobs will be calculated from the *Work and Residence History Questionnaire*. Because subjects reported time to the nearest year, jobs were assumed to begin and end in the midpoint of the year (July 1). When multiple jobs were reported within

a year, follow-up time was equally divided between the specific jobs (e.g. two jobs were assigned 0.5 year duration each, three jobs were assigned 0.33 year duration). The number of years worked before and after 1960 will be considered to account for the increased use of engineering controls and personal protective equipment in the 1960s and later.

A total of 2,876 person years of uranium mill employment was reported by the 256 former mill workers. The earliest year of employment in a vanadium or uranium mill was 1936. Several subjects were still employed in mills at the time of interview in 1999. Sixty percent of the reported work experience falls within the 1947 to 1971 period of interest defined by the congressional legislation mandating this study (Public Law 103-139). Preliminary analyses indicate the mean number of total years employed in mills was 11.2 (10.3 years SD) and ranged from 1 to 44 years. The mean number of years employed before 1960 was 3.2 (3.7 years SD) and the mean number of years employed after 1960 was 8.0 (9.1 SD).

The distributions of person years worked in specific production areas of the mill are presented in Table 2. The three largest represented categories of experience are Maintenance, Operations Supervision, and Laboratory. Fifty-six percent (143 of 256 subjects) reported some employment in Manual Labor, a typical entry level position. Eighteen percent (47 subjects, 107 total person years) reported some work in Crushing and Sampling where potential exposure to silica dust is expected to be heaviest. Experience in yellow cake Drying and Packaging, where exposure to concentrated uranium product is probably greatest, was reported by 12% of the former mill workers (31 subjects, 59 total person years).

The validity of this self-reported information will be examined by comparison against employment records collected from uranium companies. The completeness of this evaluation is limited by detail recorded in personnel records that were primarily maintained for the purpose of payroll and pension. For example, personnel records may indicate time worked as an operator first class at a specific mill, but do not indicate the specific job, duties, or area of the mill where the work occurred. Further, personnel may have worked at uranium ore processing facilities for which we do not have employment records. Despite these limitations, the comparison of self-reported work histories with available personnel data will at least inform us of the validity of recalled dates and location of work. This comparison will be performed on a random sample of 50 subjects.

Categorical measures of exposure will include cumulative years of employment in the mills, cumulative years of employment in specific production areas of the mills, cumulative years of employment in job titles, and epoch of employment (1960 and earlier, after 1960).

Analysis of exposure records from the mills may allow the linking of job histories with area measurements of total dust and radon progeny. The UNM investigators will collaborate with industrial hygienists at NIOSH to review and analyze company monitoring data on exposures associated with job titles, mill locations/departments/operations, and control technologies.

NIOSH investigators have located exposure records, of varying completeness and quality, for many of the mills included in this study. The available data include area and breathing zone concentrations of silica dust and uranium. Silica exposure data weighted for time spent in specific areas are also available.

Using available records, airborne silica and levels will be characterized by major mill area (crushing and grinding, extraction, precipitation, drying and packaging - see Merritt 1971) and calendar time. Concentrations may also be characterized by smaller areas within the major mill areas (e.g., ore sampling in the crushing and grinding area, yellowcake-barreling area of the precipitation, drying and packaging area).

It may be feasible to assign quantitative estimates of exposure by job title by considering available information related to areas worked by former millers with a given job title. Other data elements, provided that information is available, that may be considered in assigning quantitative estimates of exposures include 1) specific tasks, 2) changes in processes (materials, work practices, and implementation of engineering and/or administrative controls), 3) frequency of exposure (e.g., continuous, daily, weekly), 4) certainty of exposure (e.g., possible, probable, or definite), and 5) use of personal protective equipment.

If it is not feasible to develop quantitative estimates of exposure by job title, development of qualitative measures of exposure (present/absent; high/medium/low) by job title will be considered.

If quantitative exposure estimates are developed, information on the variability of exposure within a job title, work area, and across time will be used to assess measurement error and the potential for bias associated with misclassification of exposure status.

Data Management

The entry and processing of questionnaire and clinical data followed protocols currently in place at the Epidemiology and Cancer Control Program. Each participant was assigned a unique identification number with check digit. Before submission for keyboard entry, original data sheets were proof read, and corrections to queries will be initialed and dated (on the original). During keyboard entry, the allowed range of values for each data field was restricted, and skip patterns guided key entry (Epi Info Version 6.04B). Entered values were sight verified against the original. After entry, data files were converted to SAS data sets (Version 6.12, SAS Institute, Cary, NC) and programs were run to verify the consistency of responses within and across data sources for each subject.

Data Analysis

Conventional approaches will be used to analyze this cross-sectional data, including stratified and multivariate analyses. We will initially compare the pulmonary and renal measurements for the worker and the reference groups using Student's t-tests and chi-square statistics. Stratified analyses and multivariate modeling will be used to identify and control for confounders (e.g., age, race/ethnicity, smoking, diabetes, hypertension). For dichotomous outcome variables (e.g., cough, phlegm, wheeze, profusion, restrictive lung disease, obstructive lung disease), conditional logistic regression models will be used for multivariate estimation of odds ratios. Continuous outcome variables (e.g., FEV1, FVC, amino acids and enzyme levels in urine) will be analyzed using multivariate linear regression. These statistical techniques will provide simultaneous control for potential confounders (e.g., age, height, cigarette pack years, diabetes) and allow calculation of odds ratios for the effects of mill work variables.

The submission of manuscripts developed by UNM will be coordinated with those developed by NIOSH on exposure assessment and mortality.

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Principal Investigator

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Memorandum

Date: October 18, 2002

jen From: Lee M. Sanderson, Ph.D., Program Official *Stephanie Shack*
Office of Extramural Programs, NIOSH, E-74

Subject: Final Report Submitted for Entry into NTIS for Grant 1 U60 CC614568-01.

To: William D. Bennett
Data Systems Team, Information Resources Branch, EID, NIOSH, P03/C18

The attached final report has been received from the principal investigator on the subject NIOSH grant. If this document is forwarded to the National Technical Information Service, please let us know when a document number is known so that we can inform anyone who inquires about this final report.

Any publications that are included with this report are highlighted on the list below.

Attachment

cc: Sherri Diana, EID, P03/C13

List of Publications

rec 10/30/02

Title: Epidemiologic Studies to Evaluate Health Effects of Uranium Milling
Investigator: William E. Lambert, Ph.D.
Affiliation: University of New Mexico
City & State: Albuquerque, NM
Telephone: (505) 272-0447
Award Number: 1 U60 CC614568-01
Start & End Date: 9/30/1997–9/29/2001
Total Project Cost: \$0,000
Program Area: NORA
Key Words:

Final Report Abstract:

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In a previous study (Dawson, Madsen and Spykerman 1997), former uranium mill workers have voiced serious concerns about a broader range of health problems and impacts on quality of life). To investigate the potential impact of uranium mill employment on health-related quality of life, the following hypotheses will be tested: The mean scores for quality-of-life batteries are lower in the sample of former uranium mill workers relative to the sample of reference subjects.

Quality-of-life measures are correlated with reduced spirometric lung function.

Quality-of-life measures are correlated with reduced renal function as reflected in urinary biomarkers.

Quality-of-life indices decrease with increasing number of years of work in uranium mills.

Publications

No publications to date.