Beta-2-Microglobulin: Renal Biomarker of Workplace U Exposure
NIOSH 1 R01 OH007976-01
Final Progress Report

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NIOSH 1 R01 OH007976-01
Project Dates: December 18, 2003 – September 29, 2006
Report Date: December 5, 2008

Project Sponsor
National Institute of Occupational Safety and Health
Centers for Disease Control and Prevention

Project Director: Steve Ahrenholz, PhD

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Abstract

This study explored uses of beta-2-microglobulin as a biomarker for uranium exposure using a laboratory data and occupational history information previously collected from a population of over 2200 workers. Clinical reference intervals for this exposed population were calculated using traditional and recently developed methods incorporating outlier detection and a robust approach. Uranium exposure was characterized by several approaches. NIOSH developed estimates for job title specific exposure levels will be used in conjunction with calendar year, duration and length of employment to assign one measure of exposure to each worker. Site work location for each period of employment was used to assign a probability of exposure to several different chemical forms of uranium present at the site. In statistical analyses designed to evaluate the association between parameters of uranium exposure (amount, duration, age at exposure and chemical form) and level of urinary beta-2-microglobulin, we found that urinary log beta-2-microglobulin was associated with total cumulative exposure to uranium ($p<0.0001$). Log of serum BUN and creatinine, and plasma glucose, were not associated with uranium exposure. Age and gender were included in all models, and were significant parameters for serum BUN and creatinine, and plasma glucose, but not urinary beta-2-microglobulin. Both urinary protein and occult hematuria were significantly associated with uranium exposure.

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Accomplishments of this research project, from September 30, 2003 to September 30, 2006 are described under each Specific Aim.

This research project primarily involves analysis of previously existing data from the Fernald Workers Medical Monitoring Program (FWMMP) and the production and exposure monitoring records of the Fernald contractor.

a. Specific Aims have not been modified since original submission of the research proposal.

1. **Characterize the beta-2-microglobulin levels of a population of 2214 workers, occupationally exposed to uranium, and to compare their beta-2-microglobulin levels to reference intervals established for a population of unexposed community residents from the same region. Evaluate the trend over time in workers with repeated measures, and the ability of beta-2-microglobulin to predict diminished renal function.**

2. **Describe the relationship between beta-2-microglobulin and other parameters of renal function (serum creatinine, blood urea nitrogen, urinary protein, blood and glucose in urine) and compare those relationships in workers to the unexposed population.**

This study explored uses of beta-2-microglobulin as a biomarker for uranium exposure using a laboratory data and occupational history information previously collected from a population of 2214 workers. Level of beta-2-microglobulin in this exposed population was be compared to reference intervals calculated from data of unexposed community residents using traditional and recently developed methods incorporating outlier detection and a robust approach. Laboratory test results were on paper copy in charts, but had never been data entered. We double data entered, with verification, these laboratory test on 1686 FWMMP program participants.

Mean beta-2-microglobulin was 156.9 ug/L (sd. 773.64), and 88.1 ug/L for males (sd. 288.2) and 66.0 ug/L for females (sd. 842.7). In our analyses, we found that 22% of production workers had levels of B2M above the age- and gender-specific reference intervals calculated from the sub-population of community residents who had not received exposures beyond background. Levels of B2M were associated with the presence of microscopic hematuria and serum creatinine, but not BUN and urinary protein. Mean levels of blood urea nitrogen (BUN) were 16.1 mg/dl (males, 16.5, females, 14.3); serum creatinine, 1.02 mg/dl (males, 1.06; females, 0.82); and plasma glucose mg/dl 106.2 (males, 108.7; females, 94.3). Over 7% of the population had some amount of blood detected in their urine, and 6.5% had some amount of protein detected in their urine.

3. **Characterize the historical uranium exposure to each worker by amount and duration of exposure, age at exposure, and chemical form of uranium.**

We conducted an extensive search for additional production related documents and historic uranium monitoring data from numerous Fernald air sampling survey reports. Air sampling reports (available only for the years 1955-1968) also were obtained, which allowed us to identify workers with high exposures, and high urine uranium levels at the time of sampling. These data assisted us in our exposure reconstruction, for both usual exposures and provided the data necessary to identify short duration high intensity tasks. We used these exposure data to

develop quantitative estimates for job title x year and task x year job exposure matrices. After 1968, the site stopped using routine airborne radioactive particulate monitoring to identify jobs and areas with high radiation levels.

Uranium exposure has been characterized by several approaches. NIOSH developed estimates for job title specific exposure levels which we have used in conjunction with calendar year, duration and length of employment to assign one measure of exposure to each worker. To apply these estimates to participants of the FWMMP, we developed a complete work history file for all FWMMP participants, containing multiple job history records for each former Fernald worker. We began by using contractor work history files obtained from NIOSH, which contained information about assignment to departments, plants, job titles and associated dates (multiple record per worker format). We devised an algorithm for assigning a job title to records that did not have that designation (using plant and department information for that time period, previous job title, and codes for type of record change).

We have computed cumulative uranium exposure estimates based on NIOSH plant/job title specific estimates and the job titles assigned to our FMMP participants. We also have used these records to assign workers to exposure to certain chemical forms of uranium, such as uranium metal, or uranium oxides and salts, or uranyl nitrate. We attempted to develop a metric to assign exposures to high exposure intensity but short duration tasks, but found that the effort to do this was beyond the scope of this project.

4. **Determine the exposure-effect relationships between parameters of uranium exposure and the level of urinary beta-2-microglobulin, and levels of other measures of renal function.**

In statistical analyses designed to evaluate the association between parameters of uranium exposure (amount, duration, age at exposure and chemical form) and level of urinary beta-2-microglobulin, we found that urinary log beta-2-microglobulin was associated with total cumulative exposure to uranium ($p<0.0001$). Log of serum BUN and creatinine, and plasma glucose, were not associated with uranium exposure. Age and gender were included in all models to test the exposure effect, and were significant parameters for serum BUN and creatinine, and plasma glucose, but not urinary beta-2-microglobulin. Both urinary protein and occult hematuria were significantly associated with uranium exposure.

5. **Relate current urine uranium levels of 100 workers to historical uranium exposure and beta-2-microglobulin level.**

This pilot study of urine uranium levels was used to screen for current body burden, and related these levels to the predicted cumulative and peak uranium exposures, and, for a few workers, relate current urine uranium levels to those published in the sampling reports. We collected urine samples for analysis of uranium levels 103 former Fernald plant workers. These samples were analyzed at the Armed Forces Institute of Pathology, Washington, DC. We now have some evidence of ongoing internal uranium exposure to the kidney (urine uranium levels) via resorption, and can relate these levels to levels of urinary beta-2-microglobulin, indicating proximal tubule damage when elevated.

b. Studies and Results:

Findings to data include:

- Uranium exposure estimates are related to urinary levels of beta-2-microglobulin.
- We did not find a strong relationship between urinary beta-2-microglobulin and chronic renal disease or renal cancer. The number of cases of renal cancer was insufficient to reach statistical significance. Regarding chronic renal disease, we believe that we did not have the data necessary to adequately control for co-morbidity, such as diabetes mellitus.
- Estimated exposure to uranium may be related to elevated plasma glucose levels, in persons without diagnoses of diabetes mellitus. One of our graduate students is pursuing this analysis.
- Urine uranium levels (current) and health effects may be related to genetic variants in metal metabolizing enzymes. If we can obtain funding, we will pursue obtaining blood biospecimens for DNA isolation and analysis of genetic variants of such as the cytochrome P450 enzymes involved in vitamin D metabolism in liver and kidney, which have been shown to affect vitamin D target genes levels.

c. Significance:

The National Occupational Research Agenda (NORA) lists "Exposure Assessment Methods" and Surveillance Research" as two of the top 21 research priorities (NORA website). Usefulness o fbeta-2-microglobulin as a marker of early, preclinical damage to the proximal tubule is unclear. Industrial exposures to heavy metals such as uranium in the 1930's to the 1960's far exceeded today's limits. Workers of this era may have no residual effects, or may have some degree of permanent damage to their proximal tubules. If bone body burden is remobilized to the kidneys, ongoing internal exposure may have persisted throughout the years. Understanding risk of renal disease and usefulness of beta-2-microglobulin as a biomarker will improve medical screening and intervention in aging US population workers with previous occupational uranium exposure.

d. Future Plans:

1) Preparation of manuscripts (see below).

2) Abstract submission to Late Health Effects of Ionizing Radiation meeting at Georgetown University on May 4-6, 2008. We plan to submit two abstracts to this meeting. "Comparision of uranium exposure estimates, urine uranium levels and urinary beta-2-microglobulin in workers at a uranium processing plant and residents from the surrounding community" will describe the range of exposures and consequent health effects, measured by the biomarker of renal proximal tubule functions, beta-2-microglobulin. "Renal and breast cancer in a population of workers at a uranium processing plant and residents from the surrounding community" will focus primarily on the incidence of these cancers in community residents, but will also refer to the incidence in the Fernald workers' medical monitoring program. The size of the cohort in the Fernald workers' medical monitoring program, and the lack of resources for medical record follow-up, preclude an analysis using data with a high level of incident cancer ascertainment.

Publications and Manuscripts in Preparation:

"Urinary beta-2-microglobulin and urine uranium: Relationship to work with various chemical forms of uranium." In preparation, and expected to be submitted to a journal in in Spring, 2009.