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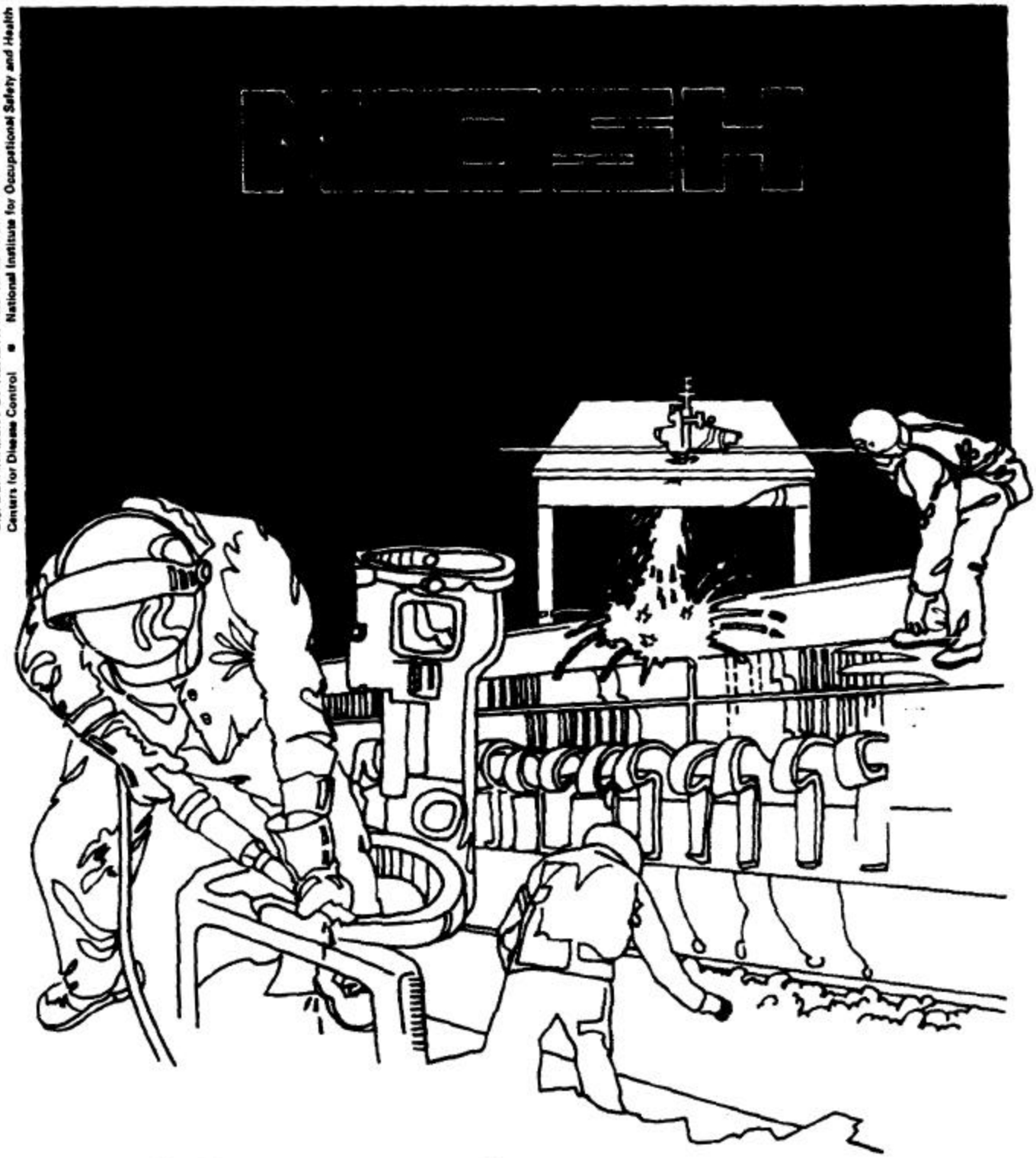

# Health Hazard Evaluation Report

HETA 86-381-1934
NUCLEAR FUEL SERVICES
ERWIN, TENNESSEE

## PREFACE

The Hazard Evaluations and Technical Assistance Branch of NIOSH conducts field investigations of possible health hazards in the workplace. These investigations are conducted under the authority of Section 20(a)(6) of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6) which authorizes the Secretary of Health and Human Services, following a written request from any employer or authorized representative of employees, to determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found.

The Hazard Evaluations and Technical Assistance Branch also provides, upon request, medical, nursing, and industrial hygiene technical and consultative assistance (TA) to Federal, state, and local agencies; labor; industry and other groups or individuals to control occupational health hazards and to prevent related trauma and disease.

Mention of company names or products does not constitute endorsement by the National Institute for Occupational Safety and Health.

HETA 86-381-1934
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NUCLEAR FUEL SERVICES
ERWIN, TENNESSEE

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## I. SUMMARY

In May 1986, the Nuclear Regulatory Commission (NRC) requested assistance from the National Institute for Occupational Safety and Health (NIOSH) in investigating complaints of kidney disorders in workers at Nuclear Fuel Services (NFS) in Erwin, Tennessee. Concern about the renal toxicity of uranium centered upon exposures prior to 1970, when the plant processed low-enriched uranium and thorium.

NIOSH investigators conducted a preliminary questionnaire survey in November 1986, comparing male senior (20+ years employment) current NFS workers to unexposed guards of similar age. NFS workers reported more frequent kidney stones (19%) and urinary tract infections (28%) than did the guards (7% and 12% respectively). The results were described in an interim report in February 1987.

A more extensive questionnaire and medical survey, in January 1988, compared current urinary abnormalities in senior NFS workers to dairy workers from a nearby town. Seventy-six current and former NFS workers participated (89% of active hourly). Fifty (98%) eligible dairy workers completed the questionnaire and 37 (79%) underwent medical testing.

The dairy workers reported kidney stones more frequently (26% vs. 21%) and infections less frequently (20% vs. 30%) than did current and former senior NFS workers; neither difference was statistically significant. Kidney function was similar in the dairy and NFS production workers. Compared to U.S. males, both groups had an unusually high lifetime prevalence of kidney stones, treatment for urinary tract infections, and high serum uric acid, a risk factor for gout. Workers in both groups had frequent risk factors for kidney stones, particularly high calcium, oxalate, sodium, uric acid, phosphorous, and low urinary volume.

Based on these results, the NIOSH investigators conclude that occupational exposures have not caused persistent, currently detectable, urinary tract disorders in workers at NFS. Several health problems related to kidney disease are unusually common in both NFS workers and in dairy workers from a nearby plant. These apparently reflect a regional rather than an occupational problem. The report discusses the study's limitations and recommends further effort to understand and prevent kidney problems in the region.

KEYWORDS: SIC 2819 (uranium, nuclear, renal, kidney, nephrotoxicity)

## II. INTRODUCTION

In May 1986, the U.S. Nuclear Regulatory Commission (NRC) requested assistance from the National Institute for Occupational Safety and Health (NIOSH) in investigating complaints of kidney disorders in workers at Nuclear Fuel Services (NFS) in Erwin, Tennessee. Kidney disease was of particular interest because uranium processed by the plant is known to be nephrotoxic,[1-4] and because NFS workers had expressed concern about kidney problems to their union, the Oil Chemical and Atomic Workers Union (OCAW), Local 3677.

NIOSH investigators met with the NRC in July 1986, and reviewed the history of the industrial process at NFS. Prior to 1970, NFS processed large amounts of low-enriched uranium and thorium. Renal exposures were presumably much higher in these early years because more stringent control measures were required after 1970, when the plant phased out the low-enriched operations and expanded production of highly enriched nuclear materials. Materials that have been enriched in U-235 are usually controlled to exposure levels well below those which cause renal toxicity, because of their radiation hazard.

In November 1986, NIOSH investigators visited NFS and conducted a questionnaire survey addressing perceived kidney problems. Current male NFS workers (with 20 or more years seniority) reported more frequent kidney stones (19%) and treatment for urinary tract infections (28%) than did male security workers employed by a contractor at NFS since 1972. Among male guards age 40-65, the lifetime prevalence (cumulative incidence) of kidney stones or treatment for urinary tract infections was 7% and 14%, respectively. Nearly all of the guards were born near Erwin and lived there currently, but many had been away for at least twenty years in previous military service. Results of this survey were described in a report destributed in February 1987.

To further define whether NFS workers have more frequent or more severe urinary tract disorders than males in the surrounding community, we subsequently conducted a more extensive medical study comparing urinary tract disorders in NFS workers to those in male dairy workers employed at a nearby plant.

## III. BACKGROUND

### A. History of the industrial process

NFS is presently the sole producer of nuclear fuel rods for the U.S. Navy. It began operations in 1957 as part of the Grace Company, was owned subsequently by the Getty Oil Company, and was purchased in 1987 by private investors. It is licensed by the NRC. The hourly workforce of approximately 500 workers is represented by the Oil, Chemical, and Atomic Workers Union.

The major operations at NFS involve the production of highly enriched uranium fuel for naval nuclear reactors and the recovery from scrap of

low enriched uranium for commercial light water reactors. Highly enriched uranium hexafluoride ($UF_6$) is converted to oxides and ultimately into finished nuclear fuel. The scrap generated from this process is reclaimed on site in a separate building. Low-enriched scrap from commercial companies is recovered in a low-enriched scrap recovery facility.

In the past, NFS has processed depleted and natural uranium, thorium, U-233, and plutonium. Uranium and thorium were converted to metal and oxides in a facility that remains on site and has never been decontaminated or decommissioned. Thorium oxide was mixed with uranium 233 to make the light water breeder reactor fuel for the Shippingsport, Pennsylvania reactor. Plutonium processing ceased in 1970, and the plutonium facility was largely decontaminated but not decommissioned. The plutonium contaminated waste remains onsite.

All information about the chemical forms of uranium currently being processed has been classified since 1985. However, since 1970, NFS has primarily processed materials of moderate to low solubility which are enriched in U-235. Prior to 1970, NFS processed primarily low-enriched uranium and thorium, materials for which chemical toxicity exceeds the hazard from radiation.

Neither personnel nor exposure records provide quantitative estimates of individual exposures prior to 1970. Personnel records are uncomputerized and of uncertain quality. Workers moved frequently from one operation or department to another. Operations may involve exposure to several levels of enrichment and solubility. Urine bioassay data do not clarify the extent of renal exposure, since these are recorded in units of radioactivity (disintegrations per minute per liter, DPM/L) rather than as urinary concentration (micrograms/liter). Translating these may not be possible because of the wide range of specific activity of materials being processed.

B. Known Health Effects of Uranium

Biologically soluble forms of uranium are known to be nephrotoxic.[1-4] The acute renal toxicity preferentially affects the terminal straight portion of the proximal tubule, i.e. the S-3 segment.[5,6] The spectrum of toxic effects has been studied extensively in animals, and to some extent in man, and includes morphological changes, enzymuria, glycosuria, increased excretion of amino acids and small proteins, and, at higher doses, albuminuria and acute renal failure.[1-6]

Much less is known about the chronic effects of long-term occupational exposure. In a study commissioned by the Manhattan Project in the late 1940's, Dounce et al. found increased excretion of the tubular enzyme catalase in the urine of 46 chemical workers exposed to uranium, relative to a comparison group.[7] These results were viewed as ambiguous because of uncontrolled differences in urine concentration. Clarkson and Kench measured urinary amino acid excretion in 18 workers exposed to

uranium hexafluoride ($UF_6$) and found increased excretion of total amino-nitrogen and individual amino acids among current workers.[8] Thun et al. found mild beta-2-microglobulinuria and aminoaciduria in 39 uranium mill workers compared to 36 local cement plant controls.[4] Beta-2-microglobulinuria increased with increasing length of exposure to "yellowcake", a powder containing 26-86% ammonium diuranate.

The renal toxicity observed in occupational populations has been mild compared to the severe toxicity of uranium when administered experimentally to both animals and people. The discrepancy may be in part due to dose, and in part due to the lack of sensitive field markers to detect injury to S-3, a portion of the proximal tubule less well understood than the convoluted portion, S-2. In addition, occupational exposures usually involve chemical forms of uranium that do not contain or readily produce the uranyl ion ($UO_2^{++}$). Uranyl ion is the primary transportable form of uranium in the kidney and may be the main cause of renal toxicity.[9] Uranyl ion is released from salts such as uranyl nitrate and acetate and is produced as a hydrolysis product of $UF_6$. Of these, only $UF_6$ is common in occupational settings. Although occupational exposure to $UF_6$ does occur occasionally due to accidental release of the gas, exposure to other less toxic forms of uranium is more common.

Neither kidney stones nor urinary tract infections have been previously linked to uranium or thorium exposure in the published literature. Increased kidney stone prevalence has been observed in workers exposed to cadmium.[10] A so-called "stone belt" exists in the southeastern United States,[11] although the true prevalence of kidney stones in this region compared to other parts of the country is still poorly defined. To our knowledge, no occupational exposures have been associated with urinary tract infections. The hypothesis has been proposed that red and white blood cells excreted in the urine following toxic injury from uranium might be mistakenly diagnosed as urinary tract infections. A urine culture, obtained at the time of the event, should be able to differentiate "sterile pyuria" from a true infection.

## IV. STUDY DESIGN AND METHODS

The present study is a cross-sectional questionnaire and medical survey comparing the frequency of specific urinary tract disorders and altered renal (kidney) function in nuclear workers with that in dairy workers of similar age from a nearby town. It was conducted in two phases: a preliminary questionnaire (pilot), and subsequent medical study.

Participants Workers eligible for the pilot study included (1) all active, disabled or retired male workers employed by NFS for at least 20 years, and (2) male guards, age 40-65, employed by the Murray Guard Company at NFS. Those eligible for the medical study included all of the above, plus a second comparison group of 50 male dairy workers from a nearby milk plant. The dairy was selected as a non-uranium local

comparison plant because of its size (approximately 50 male hourly employees, aged 40-65), its location (30 miles from NFS), because of the absence of current occupational exposure to heavy metals or solvents, and because both management and workers agreed to the study. Both the NFS and dairy workers had resided in small towns or farms in the immediate area for most of their lives.

Eligible participants were identified from lists from the respective employers. The number of potential participants, categorized by current employment status, is shown in Table 1. Fifty-one male hourly workers, age 38-65, were currently employed at the dairy. Participation in the questionnaire is computed based upon all eligible workers; participation in the medical testing is based upon workers present (at or within reach of the plant) during the days when the study was conducted.

Exposure classification Participants were classified into five groups reflecting their lifetime potential for exposure to low enriched uranium and thorium. In decreasing order these were: (1) NFS current ever-production workers (highest potential exposure) defined as current NFS workers with at least 20 years employment and at least 6 months in a production area prior to 1970, (2) NFS former workers (high potential exposure), defined as retired or disabled senior workers employed in either production or office areas, (3) senior NFS non-production workers (low or medium exposure), defined as senior workers never assigned to production but potentially exposed during strikes or through general contamination of the plant), (4) guards (minimal exposure), and (5) dairy workers (no occupational exposure). Current NFS workers were classified by senior NFS salaried and hourly workers prior to the analysis. Former workers are analysed separately because they represent a range of exposures and include workers who retired for medical reasons unrelated to uranium.

Data Collection included a questionnaire, measurement of height, weight, blood pressure, sampling of blood and urine for several measures of kidney damage or dysfunction, and measurement of uranium in urine.

Both the pilot study and medical questionnaire included five questions about recognized kidney problems (Appendix A). The more extensive medical study questionnaire also asked about risk factors for kidney and lower urinary tract disease (diabetes, hypertension, instrumentation, prostatic disease, use of phenacetin and other analgesics, smoking, "moonshine", length of residence near Erwin, family history of stones or urinar tract infections (UTI), and occupational and recreational exposures to heavy metals and solvents). Information on age and reported kidney problems (Appendix A) is available on nearly everyone. Information on other risk factors is available only for participants in the medical study.

We sought to confirm all questionnaire reports of urinary tract problems except those experienced in childhood (under age 18), in the military, or if the physician was deceased or had no current address where records

were maintained. For approximately 80% of stones and 60% of UTI, a physician visit could be documented. The medical data are highly variable in quality, however. We do not attempt to differentiate in this report between patient-reported and physician-confirmed problems.

Clinical and laboratory tests are listed in Appendix B. Blood pressure is an extraneous factor that may cause or result from nephropathy. Markers of current urinary tract infection are (1) pyuria (counted in our study as the number of white blood cells (WBC) per 10 high power fields, (2) bacteriuria (as measured in quantitative urine culture), or (3) any white cell casts in uncentrifuged urine. (For comparison, the conventional definition of UTI is >100,000 colonies of a urinary pathogen cultured per ml of sterile urine). Microscopic abnormalities indicative (but not diagnostic) of other renal disorders are hematuria, red cell or hyaline casts, or renal tubular epithelial cells. Markers of renal tubular function include urinary excretion of B-2-microglobulin (B-2), retinol-binding protein (RBP), aminoacids (measured as alpha amino nitrogen), calcium, and phosphate. Excretion of these increases as tubular function decreases. Indices of renal tubular injury (recent cellular damage) include the urinary enzymes N-acetyl glucosaminidase (NAG), and lactic dehydrogenase (LDH). Measurements reflecting glomerular function are serum creatinine (which increases as glomerular filtration rate decreases) and urine albumin (which increases either with abnormal glomerular permeability to macromolecules or with impaired tubular function).[12]

Collection proceedure Blood pressure was measured by a single trained observer, using a mercury sphygmomanometer. Triplicate readings were taken on the right arm of seated resting subjects. A clean urine specimen was collected for microscopy and quantitative bacterial culture following standard cleaning of the glans with nonbacteriostatic soap. Hyaline and granular casts were counted per ten low power fields (LPF) and WBCs and RBCs were counted per ten low power fields (HPF) in the sediment of urine centrifuged for five minutes. A routine "spot" urine was collected for urine chemistries, and a 24-hour urine specimen was collected for analytes related to kidney stone formation (Appendix B). For the NFS workers, urine was collected for uranium concentration following a weekend. Twenty milliliters of blood was obtained for serum chemistry determinations (Appendix B).

Laboratory methods Serum and urine ß-2 were measured by radioimmune assay (Pharmacia, Piscataway, NJ, 1986), RBP by radial immunodiffusion (LC-Partigen, Behring Diagnostics, LaJolla, CA), total free aminoacids as alpha amino nitrogen,[13] total calcium by modified o-cresolphthalien, and creatinine by modified Jaffe method. Serum and urine creatinine, total calcium, inorganic phosphorous, total protein, and uric acid were measured using the Dupont Autoanalyser (Dupont ACA, Wilmington, DE),[14] as were serum albumin and glucose. Urine albumin was measured by modified ELISA.[15] Serum and urine LDH were measured by the conversion of lactate to pyruvate,[16] urinary enzymes AAP and GGT by COBAS BIO centrifugal analyser,[17] NAG by modified fluorimetric assay,[18]. Analyses for the stone risk profile were performed as described by Pak[19].

Data transformation To standardize for variations in serum concentration and urine volume, we expressed B-2, RBP, and alpha amino nitrogen excretion both as ug/gram creatinine and as fractional excretion.[12] Both of these increase as tubular function declines. Fractional excretion provides the best measure of the degree of tubular impairment, and is computed as (urine B-2/plasma B-2) / (urine creatinine/plasma creatinine). Albuminuria is expressed as mg albumin/mg creatinine, as proposed by Ginsberg and others.[20,21] Tubular reabsorption of phosphate (%TRP) and of calcium (%TRC) are used to express the tubular handling of these substances, and are computed as the product of (1 - fractional excretion) x 100. Body mass is expressed as the Quetelet index [weight (kg)/ height $(m)^2$]. Body surface area ($m^2$) is computed as [weight $(kg)^{0.5378}$ x height $(cm)^{0.3964}$ x 0.024265].[22] Two variables were estimated using measurements from both "spot" and 24-hour urine collection. Twenty-four hour total protein was estimated as spot concentration (mg/g creatinine) x total creatinine in 24-hour sample (g/day). Creatinine clearance was computed as (urine creatinine x urine volume)/ (plasma creatinine x 1440 min/day x body surface/1.73 $m^2$).

Analyses involving concentrations in serum and spot urine samples used logarithmic transformation to approximate a normal distribution; those involving 24-hour collections (stone risk factors) used untransformed data.

Statistical analyses- For the questionnaire data, we compared lifetime prevalence of reported urinary tract problems in NFS workers to prevalence in the unexposed (dairy) workers. For medical parameters we compared the mean value in current NFS ever-production workers to that in the dairy workers. Data on guards (security workers at NFS) and various external referrent populations are presented for comparison but are not used in statistical testing.

Significance testing used chi-square to test association between dichotomous variables and Student's t test to test the difference between group means for continous variables. Fisher's exact 2-tail test was used to test proportions based on small sample size.

To assess dose-effect relationships, we first used Pearson correlation coefficients to screen all continuous renal outcomes against four exposure variables. These were: (1) years of NFS production work, (2) years of NFS production work prior to 1970, (3) total years at NFS (reflecting time in the general plant environment), and (4) current urine uranium. Correlations with p-value under 0.1 were further examined to determine whether the direction of association was consistent with the expected effect of a renal toxin. When both conditions were met ($p<0.1$ and trend in the appropriate direction), associations were tested further using stepwise multiple linear regression. For dichotomous renal outcomes (kidney stones and urinary tract infections), dose-response relationships were tested using unconditional logistic regression.

## V. EVALUATION CRITERIA

No industrial hygiene monitoring was conducted in this investigation, nor did NIOSH investigators attempt to assess historical exposure data. Measurement of urinary uranium reflects the potential kidney toxicity of current exposures but does not provide information about the adequacy of protection from radiation. No legal standard defines a "safe upper limit" for uranium in urine. A draft NRC document recommends that urine concentrations should not exceed 30 ug/L (126 nmol/L), and that concentrations above 15 ug/L should trigger administrative controls.[23] This recommendation applies only to uranium mill workers, however, and has never been promulgated. Spoor has reviewed the evidence on which these tolerance limits are based.[24] The NRC is presently considering a more stringent upper limit for uranium in urine.[25]

## VI. RESULTS

Participation Table 1 shows the number of workers participating in the questionnaire and medical studies. Nearly all eligible workers (98-100%) provided questionnaire information on age and the questions in Appendix A. Participation in the medical testing was lower, ranging from 89% in NFS active hourly workers to 24% in guards. As stated, participation in the medical study is computed based upon workers who could be present at the plant during the days of testing. Guards were excluded from the medical analyses because of low participation. Fifty-three (75%) current "ever-production" NFS workers participated, as did 37 (79%) current dairy workers.

Questionnaire Study Table 2 presents the number and age distribution of currently employed questionnaire respondents. All groups of current workers were similar in age to the guards and dairy workers. All were male, and only one was non-white. The 22 former NFS workers (not shown) were substantially older than the dairy workers (mean 63.0 v.s. 52.2, range 44-70, p 0.0001).

Table 3 shows the responses to the questions in Appendix A. Both the NFS and dairy workers reported an unusually high lifetime prevalence of kidney stones and infections compared to the guards and US male participants, age 40-65, in the National Health and Nutrition Examination Survey (NHANES)[26]. NFS workers were slightly below the dairy workers with respect to kidney stones (19-25% vs. 26%), and a slightly above for UTI (24-33% vs. 20%). Neither difference was statistically significant. The data on blood and protein in urine are difficult to interpret, since no comparable NHANES data exist for these questions and since the NFS workers participate in annual urine screening, whereas the dairy workers do not.

Tables 4 and 5 present more extensive questionnaire, body measurement, and exposure data for workers participating in the medical study. NFS ever-production workers are similar to the dairymen in age, body size, tobacco smoking habits, and residential history (Table 4). On average the NFS workers had worked at the plant for 25.8 years (range 20-31). Most of their experience had been in production areas of the plant, with an average of 7.7 years prior to 1970 when renal exposures to uranium were highest.

As seen in Table 5, the NFS workers reported more frequent urinary tract instrumentation (26% vs. 14%), family history of UTI in male relatives (14.6 vs. 2.0%), use of "moonshine" liquor (65% vs. 45%), and use of analgesics daily or every other day for at least one month (40% v.s. 12%). The questionnaire asked about the frequency of urinary tract instrumentation (maximum 12 times) but not about the reason for the procedure. Occasional moonshine consumption was usually an adolescent practice; only one worker reported recent use. Although analgesic use was more frequent among the uranium workers, this represented the prophylactic use of aspirin for its antithrombotic effects, reflecting local medical practice. Few workers had ever used phenacetin containing analgesics, and none had used these compounds regularly for over 10 years. The weak association between solvents and NFS employment represents a misunderstanding of the question. This question was directed at exposure to solvents outside of work. The answers reflect more common exposure to solvents at work at NFS than at the dairy plant.

Medical outcomes- Table 6 presents the urinary microscopic findings obtained from clean-catch samples. One uranium and two dairy workers had over 50 red blood cells per 10 HPF. The uranium workers showed no evidence of greater hematuria (red blood cells) or pyuria (white blood cells) than the dairyworkers. Granular and hyaline casts were present with unexpected frequency in both groups of workers. Granular casts ($\geq$ 1) were more common in the uranium than in the dairy workers although the difference was not statistically significant (13.0% vs. 3.1%, p=0.25). Quantitative bacterial urine cultures detected E. coli in the urine of one uranium and one dairy worker. The number of colonies was small (1000 and 3000 colonies/ml respectively). Although this growth is far below the conventional criterion for clinical urinary tract infection (100,000 colonies/ml), the affected workers both had over 50 red blood cells per 10 HPF; the dairy worker also had six renal epithelial cells.

Table 7 shows selected medical data on blood pressure and renal outcomes. Average systolic and diastolic blood pressure were lower in the NFS workers than in the dairymen (borderline statistical significance). Nearly all measures of kidney function based on serum and spot urine samples were similar or slightly better in the uranium workers overall. For example, urinary excretion of B-2, RBP, aminoacids and urinary enzymes (which increase with tubular dysfunction) were equivalent or lower in the NFS than the dairy workers. This was true both for excretion expressed as concentration (per gram creatinine) or as fractional excretion. Urinary pH and specific gravity were comparable, suggesting that the uranium workers as a group have similar ability to acidify and concentrate urine. Serum creatinine (which increases as overall renal function decreases) and urinary albumin and total protein (which increase with abnormal glomerular permeability) were equivalent or lower in the uranium than the dairy workers. Mean creatinine clearance, as estimated from the 24-hour collections, was also substantially higher in the uranium workers (97.2 vs. 70.3 ml/min/1.73 $m^2$, p=0.0002). This difference probably reflects less complete collection of the 24-hour samples by the dairy workers, discussed below.

Data on calcium, inorganic phosphorous, uric acid, and urine uranium are shown in the continuation of Table 7. Urinary excretion of calcium, phosphorous, and uric acid would be expected to increase if tubular function is impaired. The uranium workers have a somewhat higher urinary calcium concentration in their spot urine samples (10.36 vs. 7.06 mg/dl, p=0.02) and in their 24-hour collection (229 vs. 191 mg/24 hours, p=0.10), but the percent tubular reabsorption of calcium is similar. Excretion of phosphorous and uric acid is not statistically different between the two groups. Problems in interpreting these data are discussed below.

Current urine uranium levels, reflecting recent exposure to uranium, are low in both the NFS and dairy workers. The average urine concentration is slightly higher in the NFS workers (borderline statistical significance). The highest level measured in samples obtained after 48 hours absence from the plant, is 0.6 ug/L, well below the lower action limit of 15 ug/L recommended by the NRC for protection against renal injury from uranium in uranium mills.[23]

Table 8 presents the data on blood pressure and selected renal outcomes categorized into "normal" and "abnormal". This format allows comparison of the frequency with which uranium and dairy workers are "abnormal" compared to external referent populations. The criteria for "abnormality" and the external comparison group vary according to outcome. For example, systolic and diastolic hypertension are defined by clinical criteria[27] and the referent group consists of white males, age 40-65, participating in the NHANES survey.[26] By these criteria, hypertension is less common in the uranium workers than in either the dairy workers and or than the NHANES data. By contrast, an elevated serum uric acid appears more commonly in both the uranium and dairy workers than in the laboratory referent population.[14] Approximately 10% of the values for serum uric acid are sufficiently high to cause gout (> 8.0 mg/dL). The higher prevalence of proteinuria (by various criteria) in the uranium workers is only apparent when the data are based upon 24-hour collections and presented categorically. It is not apparent in spot urine samples or in comparisons of group means. The highest total protein was 442 mg/day in a dairy worker. Reduced tubular reabsorption of phosphorous (< 79%) is common in both NFS and dairy workers (16.1% and 28.6%, respectively), yet in the absence of low serum phosphorous may not be medically important. None of the uranium and two dairy workers had serum phosphorous < 2.5 mg/dL. The limitations of both the 24-hour and the spot urine data are discussed below. Referent data for many of the tests used are unavailable for males in the appropriate age group.

Table 9 presents data on urinary risk factors for kidney stone formation obtained from 24-hour collections. The stone risk factor analyses exclude persons whose urine sample was judged to be incomplete (< 800 mg creatinine/day). For all substances, including creatinine and total volume, the uranium workers excrete slightly more than the dairy workers. The differences between the two groups are small and, except for sulfate, are statistically non-significant. They may in part represent undercollection by the dairyworkers.

A more important finding is the frequency with which both the uranium and dairy workers exceed the definition of "abnormal" for stone risk factors, compared to an historical comparison group of persons without stones at the Texas laboratory performing the tests.[19] Table 10 shows that the Tennessee workers (both uranium and dairy) differ markedly from the Texas norms. Their most common risk factors are increased excretion of sodium, phosphorous, oxalate, and low urine volume. Supersaturation occurs commonly for calcium oxalate, brushite, and sodium urate, all factors which promote the crystalization of calcium containing stones. Only one risk factor, supersaturation with calcium oxalate, occurs significantly more frequently in the uranium than in the dairy workers (51.9 % v.s. 30.3%. p=0.05).

Dose-Effect Relationships

Table 11 presents all Pearson correlation coefficients with associations of $p<0.1$. Several renal outcomes are associated with length of employment, production experience at NFS, or current urine uranium concentration. However, the markers that might be expected, a priori, to reflect uranium toxicity, are in general either not associated with or correlated with exposure variables but in a direction opposite to the expected trend. For example, no correlations with length of employment are seen for urinary excretion of albumin, total protein, renal enzymes, amino acids, serum creatinine, or the tubular reabsorption of calcium. Associations are seen between urinary excretion of ß-2-microglobulin and RBP, the tubular reabsorption of phosphate, and 24-hour urine volume, but the trend is in the opposite direction from that expected. Those variables which are associated with length of employment in a direction that might suggest toxicity are not those that had been suspected a priori. These include urine calcium (measured on the spot but not 24 hour collection), and several risk factors for kidney stones, as measured on the 24 hour collection. The latter are urine oxalate, sulfate, phosphorous, and potassium, and uric acid excretion and saturation. All are difficult to interpret, largely because a positive trend is also present for creatinine in the 24-hour collection. The association between creatinine and years of employment suggests that collection may have been more complete among senior NFS workers.

There was insufficient evidence of consistent exposure effect relationships to justify further multivariate modelling of the continuous outcomes. For the dichotomous outcomes, kidney stones were not associated with any of the three exposure variables. However, a history of UTI was significantly associated with years of total employment at NFS, even after adjusting for age ($ß=0.0342$, $p=0.04$). UTIs were not significantly associated with years of production work at NFS or with years of production prior to 1970.

## VII. DISCUSSION AND INTERPRETATION

Motivating this study was a concern that uranium or other industrial exposures at NFS may have caused persistent kidney disease. Our data show little evidence that the NFS workers have either more frequent or more severe renal dysfunction than the dairy workers. Rather, the data suggest that the high frequency of kidney disease experienced by the NFS workers is a regional, rather than an occupational, problem. Both the uranium and dairy workers experience frequent kidney stones, treatment for urinary tract infections, elevated serum and urine uric acid, and increased urinary excretion of substances that are risk factors for calcium kidney stones.

In discussing these data, we will address two separate issues. First is the question of whether the study is truly negative with respect to uranium, or whether some occupational associations exist that have either been obscured or examined inadequately in our analyses. Second is the issue of how strong or positive is the evidence for a regional problem. Both of these issues have implications for future control measures.

At least four considerations could cause us to underestimate renal toxicity due to uranium. First, very high exposures to unenriched uranium and thorium ceased nearly twenty years ago. Our study provides no information about past effects that are no longer evident, only about persistent effects, measureable by the tests that we used. Second, most of the workers at NFS were exposed primarily to materials of moderate or low biological solubility. Exposure to highly soluble compounds, such as uranium hexafluoride, would have been unusual. Because only crude data are available on exposure, our analysis cannot identify workers exposed to particular compounds and may have obscured a mild renal effect occurring in a subgroup of more highly exposed workers. Third, some workers with severe renal toxicity may have been unable to participate in the study, either because of early termination of employment, illness, or death. Although we have little evidence of greater renal morbidity in former workers who did participate, this remains a theoretical possibility. Fourth, as discussed in the Background section, the type of renal tubular damage caused by uranium may be relatively silent and difficult to detect using the currently available field tests for evaluating nephrotoxicity. The clinical and experimental tests used in this study have proven valuable in assessing other nephrotoxic substances but may not be the ideal markers for uranium.

The largely negative occupational findings of our study are consistent with those of a study conducted by NIOSH at the Feed Materials Production Center (Fernald Plant) near Cincinnati, Ohio.[28] In both places, NIOSH investigators studied senior employees who had worked during the years when exposures to uranium and other nuclear fuels were highest but who had relatively low current exposures. In both plants the chemical form of the uranium varied but usually involved compounds of moderate or low biological solubility. Using the same tests to detect kidney dysfunction, both studies find little evidence of persistent renal effects attributable to uranium.

The single urinary tract entity that is more common, historically, in both NFS and Fernald workers is a report of urinary tract infection. These reports are difficult to interpret, because, in many instances, urine cultures were not obtained before treatment, and the symptoms, such as burning on urination, are nonspecific. UTIs are not statistically more common in NFS workers overall (31.6% v.s. 21.0%, p=0.15) but they are significantly associated in logistic regression with total years of NFS employment, controlling for age (p=0.04). At Fernald, reports of UTI's increased with length of employment in a similar pattern. The lifetime prevalence of "kidney infection" was 10.5%, 17.5% and 21.0% in the low, medium, and high exposure groups, respectively. It is unclear how these reported UTIs relate to other urinary tract risk factors, such as more frequent instrumentation (in the NFS workers), or family history of UTIs (in male relatives of NFS workers). It is clear that the UTIs represent a mix of true urinary tract infections (cystitis and pyelonephritis), and genital infections (epididymitis, prostatitis). We do not know whether these reports represent a previously unrecognized effect of uranium, or a greater level of medical awareness, medical care, and reporting than that present in the dairy workers.

Of wider public health significance is the evidence for a regional problem that extends beyond the occupational boundaries of our study. Overall, the study participants experienced a lifetime prevalence of kidney stones of approximately 25%. Compared to an estimated national average of 7.8% among males, age 40-65, participating in the NHANES survey, this represents a three-fold increase. Endemic kidney stones are an important and potentially preventable cause of pain, morbidity, and medical expense.

The so-called "stone belt" in the Southeastern United States has been identified in at least two surveys of hospitalization for nephrolithiasis.[11,29] The second of these two surveys in 1974[29] ranked North Carolina, South Carolina, Virginia and Tennessee as second through fifth among states in terms of hospitalization for stones as the proportion of all hospital admissions. Data on the annual incidence and lifetime prevalence of stones are unavailable for most of the Nation, including the the Southeast. One expects, but cannot prove, that the same geographic stone belt that exists for hospitalizations is also present for incidence.

No cause has yet been identified for increased stone formation in the Southeast. Environmental factors that have been postulated to play a role are water softness,[30] dietary consumption of meat,[31] or carbonated beverages.[32] Two of these factors, water softness and consumption of carbonated beverages, are more common in the Southeast than in the Rocky Moutain States, where stone incidence is low.[30,32] However, the actual importance of drinking water versus particular dietary habits is still undetermined.

Perhaps the most important information of our study is the profile of stone forming urinary risk factors measured in a high-risk Southeastern community. Some of the factors promoting stone formation in this population reflect environmental (largely dietary) sources, and others suggest genetic (metabolic) predisposition. For example, the high urinary calcium, phosphorous, sodium, oxalate, and low urine volume are likely to be strongly influenced by diet.[19] Uric acid, which is increased in serum, and to a lesser extent in urine, reflects both dietary and metabolic influences.

We did not systematically collect information on diet or drinking water on all study participants. Workers told us informally that consumption of milk, dark green vegetables (collards etc.) and salted foods are common in this region. These may contribute to dietary calcium, oxalate, and sodium intake. Some information is available on drinking water in municipal water supplies for the towns in which the two plants are located. The content of sodium and water hardness (a correlate of calcium content) is extremely low in all measurements in these towns from 1982-1987. Only 13 measurements have been obtained during these years. However, the concentration of these substances would not be expected to fluctuate greatly and the measured values are consistent with published data for Tennessee.[30,33] These limited data would suggest that diet, not drinking water, contributes to the high urinary sodium and mildly increased calcium in the workers examined.

In summary, the study found an increased occurrence of kidney stones, urinary tract infections, and several factors related to kidney stone formation in both uranium and dairy workers compared to external referent populations. Future research should define the geographic range of increased kidney stone formation in the Southeast and attempt to identify its causes.

## VIII. RECOMMENDATIONS

1. In future, NFS workers who develop signs and symptoms of urinary tract infection should be thoroughly evaluated prior to treatment with antibiotics. The evaluation should attempt to differentiate between (a) true urinary tract infections (involving the bladder or kidney), (b) sexually transmitted diseases, or (c) prostatism. Culture and microscopic evaluation of urine and prostatic fluid will help to clarify the nature of these urinary tract disorders, if they continue to occur.

2. Individual workers with kidney stones or with stone-forming risk factors in their urine can prevent future stones by increasing their fluid intake. Other specific risk factors can be reduced by decreasing dietary salt (sodium), milk intake (calcium) and dark green vegetables (oxalate).

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## XI. DISTRIBUTION AND AVAILABILITY OF REPORT

Copies of this report are currently available, upon request, from NIOSH, Division of Technical Services, Publications Dissemination, 4676 Columbia Parkway, Cincinnati, Ohio 45226. After 90 days, the report will be available through the National Technical Information Service (NTIS), Springfield, Virginia 22161.

Copies of this report have been sent to:

1. Nuclear Regulatory Commission
2. NFS Inc.
3. Oil Chemical and Atomic Workers Union, Local 3677
4. Murray Guard Co.
5. PET Milk Co.
6. Oil Chemical and Atomic Workers Union, Local 3-65
7. Tennessee State Health Department
8. OSHA, Region IV

For the purpose of informing the "affected employees", the employer shall promptly post the report for a period of 30 calendar days in a prominent place near where the exposed employees work.

TABLE 1

PARTICIPATION IN THE QUESTIONNAIRE AND MEDICAL STUDY

| Employment Category | Number Eligible | Questionaire Participants Number (%) | Medical Study Participants Number (%)* |
|---|---|---|---|
| **URANIUM EXPOSED** | | | |
| NFS Active | | | |
| Hourly | 58 | 58 (100%) | 50 (89%) |
| Salaried | 35 | 35 (100%) | 19 (59%) |
| NFS Retired | | | |
| Hourly | 6 | 5 ( 83%) | 2 (40%) |
| Salaried | 10 | 10 (100%) | 2 (10%) |
| NFS Disability | 6 | 6 (100%) | 3 (50%) |
| Subtotal | 115 | 114 (99%) | 76 (69%) |
| **REFERENTS** | | | |
| Guards | 43 | 43 (100%) | 10 (24%) |
| Dairy Workers | 51 | 50 ( 98%) | 37 (79%) |

* Participation in medical study based upon number of workers available when testing performed.

TABLE 2

AGE CHARACTERISTICS OF CURRENT WORKERS COMPLETING THE QUESTIONNAIRE CATEGORIZED BY POTENTIAL FOR EXPOSURE

| Exposure Category | Exposure Potential | Number | Age | |
|---|---|---|---|---|
| | | | Average | Range |
| Ever Production | (High) | 73 | 49.3 | 41-61 |
| Never-Production | (Low/Medium) | 20 | 51.3 | 40-63 |
| Guards | (Low) | 43 | 51.2 | 40-66 |
| Dairy Workers | (None) | 50 | 52.2 | 38-65 |

TABLE 3

LIFETIME HISTORY OF VARIOUS KIDNEY PROBLEMS, QUESTIONNAIRE REPORTS

KIDNEY STONE

| Exposure Group | # Cases | Percent |
|---|---|---|
| NFS* | | |
| Ever Production- Active | 14 | 19% |
| Never Production-Active | 5 | 25% |
| Retired & Disabled | 5 | 24% |
| Guards (at NFS) | 3 | 7% |
| Dairy Workers (Near NFS) | 13 | 26% |
| N-HANES (National US) | - | 8% |

URINARY TRACT INFECTION

| Exposure Group | # Cases | Percent |
|---|---|---|
| NFS* | | |
| Ever Production- Active | 24 | 33% |
| Never Production-Active | 5 | 25% |
| Retired & Disabled | 5 | 24% |
| Guards (at NFS) | 6 | 14% |
| Dairy Workers (Near NFS) | 10 | 20% |
| N-HANES (National US) | - | 8% |

BLOOD IN URINE

| Exposure Group | # Cases | Percent |
|---|---|---|
| NFS* | | |
| Ever Production- Active | 18 | 25% |
| Never Production-Active | 3 | 15% |
| Retired & Disabled | 3 | 14% |
| Guards (at NFS) | 3 | 7% |
| Dairy Workers (Near NFS) | 7 | 14% |

PROTEIN IN URINE

| Exposure Group | # Cases | Percent |
|---|---|---|
| NFS* | | |
| Ever Production- Active | 3 | 4% |
| Never Production-Active | 1 | 5% |
| Retired & Disabled | 1 | 5% |
| Guards (at NFS) | 0 | 0% |
| Dairy Workers (Near NFS) | 1 | 2% |

* None of the differences between NFS and dairy workers are statistically significant

TABLE 4

DEMOGRAPHIC CHARACTERISTICS OF CURRENT WORKERS
PARTICIPATING IN MEDICAL STUDY

| | URANIUM EVER-PRODUCTION (N=55) | | | DAIRY WORKERS (N=37) | | | |
|---|---|---|---|---|---|---|---|
| Characteristic | Mean | (SD) | Range | Mean | (SD) | Range | p value |
| Age (years) | 49.2 | (4.6) | 42-61 | 50.8 | (9.9) | (38-64) | (0.37) |
| Height (m) | 1.77 | (.05) | 1.7-1.9 | 1.77 | (.07) | 1.6-1.9 | (0.5) |
| Weight (kg) | 87.8 | (11.6) | 64-123 | 87.7 | (17.2) | 59-135 | (0.98) |
| Surface area ($m^2$) | 2.1 | (0.2) | 1.7-2.5 | 2.1 | (0.2) | 1.7 -2.6 | (0.96) |
| Quetelet Index | 27.9 | (3.9) | 18-41 | 28.1 | (5.2) | 20-45 | (0.86) |
| Cigarettes (last 2 days) | 13.1 | (21.5) | 0-80 | 15.4 | (21.7) | 0-80 | (0.58) |
| Born within 50 miles of Erwin | 89.1% | | | 88.0% | | | (0.86) |
| Years Away from Erwin | 3.3 | (5.1) | 0-27 | 3.8 | (8.7) | 0-49 | (0.7) |
| Years Employed at NFS | | | | | | | |
| Total | 25.8 | (3.0) | 20-31 | 0 | - | - | - |
| Years in Production | 22.2 | (8.5) | 1-30 | 0 | - | - | - |
| Years in Prod. Pre-1970 | 7.7 | (4.0) | 0-13 | 0 | - | - | - |

TABLE 5

RISK FACTORS FOR URINARY TRACT DISEASE AS REPORTED ON QUESTIONNAIRE:
CURRENT WORKERS PARTICIPATING IN MEDICAL STUDY

| | URANIUM EVER-PRODUCTION (N=55) | DAIRY WORKERS (N=37) | |
|---|---|---|---|
| | Percent or Mean (SD) Range | Percent or Mean (SD) Range | p value |
| Diabetes | | | |
| (High blood sugar) | 5.5% | 6.0% | (1.0) |
| (Sugar in urine) | 12.7% | 8.0% | (0.43) |
| Hypertension | | | |
| (Ever diagnosed) | 43.6% | 43.2% | (1.0) |
| (Medicated in last week) | 20.0% | 20.0% | (1.0) |
| Urinary Tract Instrumentation | | | |
| (Ever) | 21.8% | 8.0% | (0.049) |
| (Number of times) | 0.42 (1.65) 0-12 | 0.06 (0.23) 0-1 | (0.12) |
| Family History of | | | |
| Kidney stones | 30.9% | 24.0% | (0.4) |
| Urinary tract infection | 14.6% | 2.0% | (0.034) |
| Other | | | |
| Prostatic Problems | 20.0% | 14.0% | (0.4) |
| Venereal Disease | 5.5% | 4.0% | (1.0) |
| Moonshine- Ever Used | 65.1% | 44.9% | (0.038) |
| " Used $\geq$ 10 times | 38.2% | 13.5% | (0.011) |
| Lead Exp. (Non-NFS) | 3.6% | 10.0% | (0.25) |
| Cadmium (Non-NFS) | 1.8% | 0 | - |
| Solvents (Non-Occup) | 14.6% | 4.1% | (0.098) |
| Aminoglycosides | 16.3% | 24.0% | (0.34) |
| Analgesics (Regular use) | 40.0% | 12.0% | (0.001) |
| " (Regular use > 10 yrs) | 3.6% | 0 | - |
| " (Some phenacetin use) | 7.3% | 2.0% | (0.37) |
| Antacids | 58.2% | 66.0% | (0.41) |

TABLE 6

URINARY MICROSCOPIC FINDINGS, CURRENT WORKERS

| | None | 1-10 | 11-50 | > 50 |
|---|---|---|---|---|
| Red Blood Cells (per 10 HPF)* | | | | |
| NFS Ever-production** | 49.1% | 41.8% | 7.3% | 1.8% |
| Dairy* | 40.5% | 48.6% | 5.4% | 5.4% |
| White Blood Cells (per 10 HPF)* | | | | |
| NFS Ever-production | 50.9% | 47.3% | 1.8% | - |
| Dairy | 43.2% | 51.4% | - | 5.4% |
| Casts, Granular | | | | |
| NFS Ever-production | 87.3% | 10.9% | - | 1.8% |
| Dairy | 94.6% | 5.4% | - | - |
| Casts, Hyaline | | | | |
| NFS Ever-production | 94.5% | 5.5% | - | - |
| Dairy | 89.2% | 10.8% | - | - |

* Blood cells counted per 10 high power fields (HPF)
** All analyses include 55 NFS and 37 dairy workers.

TABLE 7

SELECTED MEDICAL CHARACTERISTICS OF CURRENT NUCLEAR V.S. MILK WORKERS

| | URANIUM EVER-PRODUCTION (N=55) | | | DAIRY WORKERS (N=37) | | | |
|---|---|---|---|---|---|---|---|
| | Geometric Mean | (SD) | Range | Geometric Mean | (SD) | Range | p value |
| Blood Pressure (mm/Hg) | | | | | | | |
| Systolic (Average) | 129.0 | (1.1) | 98-173 | 136.5 | (1.2) | 105-190 | (0.05) |
| Diastolic (") | 81.8 | (1.1) | 63-118 | 86.5 | (1.2) | 71-136 | (0.047) |
| Beta-2-microglobulin | | | | | | | |
| Serum (ug/L) | 1631.0 | (1) | 984-3198 | 1973 | (1) | 2000-3142 | (0.0003) |
| Urine (ug/g creat.) | 94.2 | (2.1) | 29-469 | 118.5 | (1.9) | 40-544 | (0.12) |
| Fractional excretion $x10^4$ | 4.96 | (*) | 1-29 | 5.44 | (*) | 0.8-28 | (0.58) |
| Retinol binding protein | | | | | | | |
| Serum (mg/dl) | 5.0 | (1.3) | 2.8-7.2 | 5.3 | (1.2) | 3.2-7.2 | (0.17) |
| Urine (ug/g creat.) | 78.2 | (2.6) | 5.9-818 | 123.7 | (2.6) | 14-1357 | (0.03) |
| Fractional excretion $x10^5$ | 1.34 | (*) | 0.26-26 | 2.16 | (*) | 0.1-10.7 | (0.04) |
| Alpha amino nitrogen | | | | | | | |
| Serum (ug/ml) | 49.9 | (1.1) | 39-63 | 47.1 | (1.1) | 37-60 | (0.025) |
| Urine (mg/g creat.) | 82.6 | (1.6) | 16-202 | 88.0 | (1.5) | 22-188 | (0.50) |
| Fractional excretion $x10^2$ | 1.42 | (163) | 0.3-3.7 | 1.67 | (163) | 0.4-3.5 | (0.14) |
| Enzymes | | | | | | | |
| NAG, urine (U/g creat.) | 1.05 | (2.3) | 0.1-6.7 | 1.32 | (2.1) | 0.3-6.9 | (0.18) |
| LDH, serum (mU/ml) | 153.5 | (1.2) | 104-251 | 150.9 | (1.3) | 80-222 | (0.73) |
| " urine (U/g creat.) | 2.9 | (2.0) | 0.5-16.7 | 3.75 | (1.9) | .9-10.3 | (0.10) |
| pH, Urine | 5.6 | (0.7) | 5.0-7.0 | 5.7 | (0.9) | 5.0-8.0 | (0.52 |
| Specific gravity, urine | 1.018 | (.007) | 1.003-34 | 1.016 | (.008) | 1.003-33 | (0.36) |
| Creatinine, serum (mg/dl) | 0.86 | (1.3) | 0.3-1.5 | 0.91 | (1.3) | 0.3-1.3 | (0.3) |
| " clearance (ml/min)** | 97.2 | (1.4) | 59-226 | 70.3 | (1.5) | 22-282 | (0.0002) |
| Albumin, serum (g/dl) | 4.19 | (1.1) | 3.8-4.9 | 4.19 | (1.1) | 3.7-4.9 | (0.9) |
| " urine (mg/mg creat x .001) | 4.3 | (*) | 1.0-42.4 | 4.6 | (*) | 1.0-15.8 | (0.6) |
| Total protein, serum | 6.7 | (1.2) | 4.8-9.7 | 6.9 | (1.1) | 4.6-9.1 | (0.4) |
| " urine (mg/mg creat x .01) | 8.2 | (161) | 2.4-27.3 | 9.5 | (173) | 3.6-43.6 | (0.18) |
| " urine (mg/24 hours)** | 98.6 | (1.8) | 28-354 | 94.6 | (1.8) | 34-442 | (0.77) |

* Large standard deviations exceed 1500.

** Estimated from the 24 hour collection as described in methods section. Excludes persons with total creatinine < 800 mg/24 hours.

TABLE 7 (CONTINUED)

CALCIUM, PHOSPHOROUS, URIC ACID AND URINE URANIUM

| | URANIUM EVER-PRODUCTION (N=55) | | | DAIRY WORKERS (N=37) | | | |
|---|---|---|---|---|---|---|---|
| | Geometric Mean | (SD) | Range | Geometric Mean | (SD) | Range | p value |
| Calcium | | | | | | | |
| Serum (mg/dl) | 9.61 | (1.0) | 9.2-10.4 | 9.65 | (1.0) | 9.2-10.6 | (0.48) |
| Urine (mg/dl) | 10.36 | (2.1) | 2.5-44.7 | 7.06 | (2.0) | 2.4-26.2 | (0.02) |
| Tubular Reabsorp.(%) | 99.1% | (1.0) | 97-99.9% | 99.2% | (1.0) | 98-99.9% | (0.25) |
| Urine (mg/24 hours) * | 229 | (102) | 44-500 | 191 | (101) | 34-464 | (0.10) |
| Phosphorous, inorganic | | | | | | | |
| Serum (mg/dl) | 3.8 | (1.2) | 2.6-5.6 | 3.7 | (1.2) | 2.4-5.7 | (0.5) |
| Urine (mg/dl) | 72.9 | (2.1) | 16-325 | 63.9 | (2.0) | 16-181 | (0.4) |
| Tubular Reab.(%) | 85.4% | (1.1) | 71-97% | 79.0% | (0.24) | 10-98% | (0.24) |
| Urine (mg/24 hr) * | 1328 | (345) | 626-2189 | 1244 | (419) | 142-2024 | (0.32) |
| Uric acid | | | | | | | |
| Serum (mg/DL) | 6.2 | (1.2) | 3.5-9.3 | 6.2 | (1.2) | 4.2-8.9 | (0.98) |
| Urine (mg/g creat.x 0.1) | 3.12 | (14.2) | 1.7-7.3 | 3.25 | (14.3) | 1.0-5.7 | (0.57) |
| Fractional excretion $x10^2$ | 4.3 | (158) | 1.5-11.8 | 4.7 | (170) | 0.6-8.6 | (0.42) |
| Urine (mg/24 hr) * | 593 | (229) | 128-1434 | 513 | (224) | 149-941 | (0.12) |
| Urine Uranium (ug/L) (Current weekend sample) | 0.07 | (2.2) | 0.01-0.6 | 0.05 | (2.7) | 0.01-0.34 | (0.08) |

* Measured separately as part of 24-hour collection for stone risk factors. Data available on 54 NFS ever-production and 33 dairy workers for whom 24-hour collection considered "adequate" (creatinine > 800 mg/day).

TABLE 8

PERCENT "ABNORMAL" AMONG CURRENT URANIUM AND DAIRY WORKERS COMPARED TO EXTERNAL REFERENT POPULATIONS

| VARIABLE (DEFINITION OF "ABNORMAL") | URANIUM EVER-PRODUCTION (N=55) | DAIRY WORKERS (N=37) | EXTERNAL COMPARISON | P VALUE NFS V.S. DAIRY |
|---|---|---|---|---|
| Blood Pressure | | | | |
| Systolic (> 160 mm/Hg)[27] | 3.6% | 10.8% | 10.8%* | 0.17 |
| Diastolic (≥ 90 mm/Hg)[27] | 23.6% | 32.4% | 37.1%* | 0.35 |
| Creatinine | | | | |
| Serum (≥ 1.4 mg/dl)[14] | 1.8% | 0% | 2.5%** | 0.4 |
| Total protein | | | | |
| Urine (>0.2 mg/mg creat)[20] | 5.5% | 8.1% | N.A. | 0.6 |
| Urine (>200 mg/24 hrs)[34] | 12.7% | 5.4% | N.A. | 0.25 |
| Urine (>150 mg/24 hrs)[34] | 20.0% | 16.2% | N.A. | 0.6 |
| Urine (> 60 mg/24 hrs)[34] | 83.6% | 51.4% | N.A. | 0.01 |
| Uric acid | | | | |
| Serum (> 7.2 mg/dL)[14] | 29.1 | 24.3 | 2.5%** | 0.6 |
| " (> 8.0 mg/dL) | 10.9 | 10.8 | N.A. | 0.9 |
| " (> 9.0 mg/dL) | 1.8 | 0 | N.A. | - |
| Calcium | | | | |
| Serum (>10.2 mg/dl)[14] | 1.8 | 5.7 | 2.5%** | 0.6 |
| Phosphorous, inorganic | | | | |
| Serum (≥ 5.0 mg/dl)[14] | 5.5 | 5.7 | 2.5%** | 1.0 |
| " (< 2.5 mg/dl)[14] | 0 | 5.7 | 2.5%** | - |
| Tubular Reab.(< 79%)[34] | 16.1 | 28.6 | N.A. | - |

* Percent of U.S. males, age 40-65, above specified value[26]

** Percent of laboratory referents above specified value[14]

TABLE 9

URINARY RISK FACTORS FOR KIDNEY STONES: CURRENT WORKERS

| Risk Factor | URANIUM EVER-PRODUCTION (N=54) Arithmetic Mean (SD) Range | DAIRY WORKERS (N=33) Arithmetic Mean (SD) Range | p value |
|---|---|---|---|
| Calcium-Oxalate Supersat.* | 2.1 (1.0) 0.4-4.9 | 1.9 (1.1) 0.4-6.2 | (0.33) |
| Calcium (mg/day) | 229 (102) 44-500 | 191 (101) 34-464 | (0.10) |
| Oxalate (mg/day) | 46.3 (12.0) 22-77 | 42.6 (12) 23-74 | (0.17) |
| Brushite Supersaturation* | 2.3 (1.7) 0.14-7.05 | 2.1 (1.6) 0.19-5.82 | (0.56) |
| Calcium (mg/day) | 229 (102) 44-500 | 191 (101) 34-464 | (0.10) |
| Phosphorous (mg/day) | 1328 (345) 626-2189 | 1244 (419) 142-2024 | (0.32) |
| Sodium Urate Supersat.* | 3.7 (2.6) 0.1-10.0 | 3.2 (2.5) 0.4-11.7 | (0.30) |
| Sodium (meq/day) | 230 ( 82) 66-412 | 207 (71) 68-335 | (0.18) |
| Uric Acid (") | 593 (229) 128-1434 | 513 (224) 149-941 | (0.12) |
| Uric acid saturation | 1.4 (1.2) 0.05-5.82 | 1.2 (1.0) .06-3.92 | (0.49) |
| Struvite Supersaturation* | 5.1 (11.7) .01-76.7 | 5.0 (6.9) .02-25.5 | (0.98) |
| Other | | | |
| Citrate (mg/day) | 770 (296) 269-1656 | 696 (230) 330-1200 | (0.22) |
| pH | 6.14 (0.53) 5.1-7.7 | 6.16 (0.55) 5.0-7.2 | (0.91) |
| Magnesium (mg/day) | 133.0 (33.9) 75-226 | 128.7 (49) 57-261 | (0.66) |
| Sulfate ($SO_4$) | 24.1 (8.2) 12-45 | 19.2 (9.1) 2-40 | (0.01) |
| Potasium (meq/day) | 90.9 (66.2) 34-520 | 70.4 (26.3) 30-121 | (0.057) |
| Ammonium (meq/day) | 41.1 (11.8) 21-79 | 56.7 (114.4) 18-690 | (0.44) |
| Creatinine (mg/day) | 1674 (328) 963-2606 | 1457 (346) 863-2136 | (0.004) |
| Urine volume (L/day) | 1.79 (0.7) 0.64-3.37 | 1.69 (0.7) 0.8-3.9 | (0.54) |

* Urinary saturations of calcium oxalate, brushite (dicalcium phosphate), sodium urate, and struvite are estimated from activity products. The group means are expressed relative to the arithmetic mean of an historical referrent group of 41 healthy people without stones at the same laboratory. Uric acid saturation is the concentration of undissociated uric acid as a multiple of the mean in the same group.[19]

TABLE 10

PERCENT "ABNORMAL"* AMONG CURRENT URANIUM AND DAIRY WORKERS COMPARED TO TEXAS REFERENT POPULATION[16]

| | PERCENT "ABNORMAL"* | | | |
|---|---|---|---|---|
| RISK FACTOR (UNITS) | URANIUM EVER-PRODUCTION (N=54) | DAIRY WORKERS (N=33) | TEXAS COMPARISON (N=VARIABLE) | P VALUE NFS V.S. DAIRY |
| Calcium-Oxalate Supersat. | 51.9% | 30.3% | N.A.** | 0.049 |
| Calcium (>250 mg/day) | 31.5% | 24.2% | 2.5% | >0.2 |
| Oxalate (>45 mg/day) | 51.9% | 33.3% | 2.5% | 0.09 |
| Brushite Supersaturation | 46.3% | 42.4% | N.A.** | >0.2 |
| Calcium (>250 mg/day) | 26.1% | 21.9% | 2.5% | |
| Phosphorous (>1400 mg/day) | 68.5% | 57.6% | 2.5% | >0.2 |
| Sodium Urate Supersat. | 72.2% | 63.6% | N.A.** | >0.2 |
| Sodium (>200 meq/day) | 64.8% | 45.5% | 2.5% | 0.076 |
| Uric Acid (>700 mg/day) | 24.1% | 21.2% | 2.5% | >0.2 |
| Uric Acid Supersaturation | 20.4% | 18.2% | N.A.** | >0.2 |
| Struvite Supersaturation* | 1.9 | 0 | N.A.** | - |
| Other | | | | |
| Low Citrate (< 320 mg/day) | 1.9% | 0% | 2.5% | - |
| Low pH (< 5.5) | 11.1% | 9.1% | 2.5% | >0.2 |
| Low Magnesium (<60 mg/day) | 0 | 3.1% | 2.5% | >0.2 |
| Sulfate (>30 mg/day) | 18.5 | 9.1 | 2.5% | >0.2 |
| Low Volume (< 2 L/day) | 68.5% | 75.8% | N.A. | >0.2 |

* Abnormality defined by > 2 SD (Texas data) for all stone risk factors except pH, citrate and magnesium (< 5'th percentile) and total volume (< 2 L/day).[19]

** For activity products, abnormal defined as > twice the mean of the non-stone forming Texas referrent group (struvite= 75 x the mean).[19]

TABLE 11

CONTINUOUS RENAL OUTCOMES CORRELATED WITH NFS EXPOSURE AT P VALUE < 0.1

| | TOTAL YEARS EMPLOYMENT AT NFS | YEARS IN PRODUCTION AT NFS | YEARS IN PRODUCTION PRE-1970 NFS | CURRENT URINE URANIUM |
|---|---|---|---|---|
| | Correlation (p-value) | Correlation (p value) | Correlation (p value) | Correlation (p value) |
| Beta-2-microglobulin | | | | |
| Urine (log ug/g creat.)* | - | -0.1684 (0.063) | - | - |
| Retinol binding protein | | | | |
| Urine (log ug/g creat.)* | -0.1676 (0.069) | - | - | - |
| Fractional excretion (log)* | -0.1672 (0.072) | - | - | - |
| Calcium | | | | |
| Urine (mg/dl)* | 0.1614 (0.078) | 0.2036 (0.026) | - | 0.1844 (0.065) |
| Phosphorous, Tubular Reabsorption* | - | 0.1544 (0.092) | - | - |
| Urine (log mg/24 hr) ** | 0.1671 (0.067) | 0.1902 (0.037) | - | - |
| Uric acid (log mg/24 hr) ** | 0.1603 (0.079) | - | - | - |
| " saturation** | - | - | 0.2761 (0.01) | 0.2833 (0.011) |
| Oxalate (mg/24 hours)** | 0.1560 (0.088) | - | - | - |
| Magnesium (mg/24 hours)** | - | - | -0.1899 (0.0799) | - |
| Sulfate (mg/24 hours)** | 0.1781 (0.051) | 0.1632 (0.074) | - | - |
| Potasium (meq/24 hours)** | 0.1671 (0.067) | 0.1902 (0.037) | - | - |
| Creatinine (mg/24 hours)** | 0.2143 (0.018) | 0.1807 (0.047) | | 0.2382 (0.072) |
| Volume (L/24 hours)** | - | - | -0.2763 (0.010) | - |

* Measured on spot urine collection
** Measured on 24-hour collection

## Appendix A

### Questions on the NIOSH Questionnaire

1) Have you ever had a kidney stone (including gravel in your urine)?

2) Have you ever had blood in your urine (either that you saw or that was detected by a physician)?

3) Have you ever had protein in your urine?

4) Have you ever had an infection of your kidneys or bladder?

5) Have you ever had other kidney problems? (Please specify)

## Appendix B

## CLINICAL AND LABORATORY MEASUREMENTS IN MEDICAL STUDY

**Blood Pressure** — Systolic, diastolic

**Urinary Tract Infections**

1) Quantitative bacterial urine culture*

2) Quantitative microscopy - WBC, RBC, Casts*

**Renal Tubular Evaluation**

Proteinuria (Low molecular Weight)**
- Beta-2-microglobulin (B-2)
- Retinol binding (RBP)
- Alpha amino nitrogen

Enzymuria** Lactase dehydrogenase (LDH)
- N-acetyl glucosaminidase (NAG)

Tubular Reabsorption**
- Phosphate (% TRP)
- Calcium (24-hour excretion)

Other
- pH
- Uric acid**
- Glucose**

**Renal Glomerular Evaluation**

Proteinuria (High molecular weight)
- Albumin
- Total protein

Other
- Creatinine
- Urea nitrogen

**Risk Factors for Renal Stones*****

Calcium, oxalate, uric acid, citrate, pH, total volume, sodium, sulfate, phosphorous, magnesium, potassium, ammonium

* Clean catch sample ** Spot urine or blood samples
*** 24-hour samples