Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

URANIUM IN DRINKING WATER THE BALTINGLASS STUDY

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Note Regarding Change Of Nomenclature

This project commenced early in 2003 and was undertaken by the Department of Public Health of the then Eastern Regional Health Authority at the request of the then South Western Area Health Board.

Resulting from the re-organisation of the health services, the titles of the foregoing bodies changed with effect from the 1st of January 2005. The former Area Health Board is now titled The Health Service Executive South Western Area and the former Chief Executive Officer of same is now the Chief Officer. The former Eastern Regional Health Authority is now the Health Service Executive Eastern Region. Throughout the report the current nomenclature is used.

PREFACE

In 2002, raised levels of uranium were identified in a public drinking water supply serving part of a town in West Wicklow. As a result of local concern, the then South Western Area Health Board requested that an epidemiological study be undertaken to determine whether the exposure resulted in adverse health effects. The Department of Public Health, of the then Eastern Regional Health Authority, established a multi-disciplinary Scientific Steering Committee to undertake this investigation. This committee consisted of personnel from the Department of Public Health itself, the South Western Area Health Board, the Department of Public Health Medicine and Epidemiology, University College Dublin and The Adelaide and Meath Hospital, Dublin incorporating The National Children's Hospital.

In relation to this matter this has been the largest study of its kind internationally to date. A detailed investigation was carried out locally and the results were found to be very reassuring from a public health perspective.

I would like to thank all those who contributed to the study. I would especially like to thank the people of Baltinglass for their co-operation and patience during this undertaking. In addition I would like to pay tribute to Dr Ruth McDermott who so successfully managed the project and to her staff. Thanks are also due to Dr Gerardine Sayers for setting up the study and to Dr Howard Johnson for his help and advice.

A special word of thanks is due to Dr Gerard Boran and Professor Brian Keogh from The Adelaide and Meath Hospital, Dublin incorporating The National Children's Hospital, and to Dr Anthony Staines from the Department of Public Health Medicine and Epidemiology, University College Dublin, each of whom gave generously of their time to this undertaking and whose participation was of crucial importance.

The Scientific Steering Committee would also like to record their appreciation for the support of the Chief Officer of the Health Service Executive South Western Area, Pat Donnelly and his staff.

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Chairperson
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GLOSSARY

Beta-2-microglobulin – a protein found in urine, the level of which can be measured as an indicator of kidney tubular dysfunction

Biomarker of exposure - a substance that is foreign to the body that is measured within a compartment of an organism

Biomarkers of effect - any measurable biochemical, physiological, or other alteration within an organism that can be recognized as a potential health impairment or disease

Collagen IV – a protein excreted in urine, the levels of which are currently being considered as a potentially useful early indicator of kidney dysfunction

Creatinine - an indicator of glomerular function

Groundwater - water that is below the surface of the ground in the saturation zone and in direct contact with the ground or subsoil

Health screening – the systematic application of a test or inquiry to identify individuals at sufficient risk of a specific disorder to benefit from further investigation

Heavy metals – a group of metals that have a high atomic weight and which can exert toxic effects on the kidney

Isotope - a chemical element having the same atomic number as another (the same number of protons) but different atomic mass (different number of neutrons)

Mental Component Score, Physical Component Score– summary measures derived from responses to the short form 12 questionnaire which reflect a person's physical and mental health respectively

Orthostatic proteinuria - an excess of serum proteins in the urine caused by standing

Renal - pertaining to the kidney

Renal glomerulus - globular tuft of blood vessels which projects into the expanded end or capsule of the renal tubule

Renal tubules - minute reabsorptive canals made up of basement membrane, lined with epithelium, composing the substance of the kidney, secreting, collecting and conducting the urine

Retinol binding protein – a protein excreted in urine, the levels of which can be measured as an indicator of kidney tubular dysfunction

Spot urine - random urine sample, not collected at a particular time of day

Urea - an indicator of kidney function

EXECUTIVE SUMMARY

Introduction

In 2002, raised levels of uranium were found in one of the public drinking water supplies to the town of Baltinglass in County Wicklow. The uranium was of natural origin and came from the underlying granite rock in the area. In view of this finding and the resulting local concern, a public health study was undertaken to determine whether the exposure had led to health effects.

Background

The Environmental Protection Agency commenced a national monitoring programme of groundwater in 1995 as part of its mandate in monitoring the environment. The range of metals analysed was subsequently expanded to include uranium as well as several other metals. Analysis of samples taken during the course of the survey indicated that levels of uranium were generally low. However, raised levels of uranium (initial results varying from 120µg/L to 142µg/L) were found in one of the three wells that supplied drinking water to the town of Baltinglass, County Wicklow. The supply was discontinued and the whole town was subsequently supplied with water sourced from the other two wells.

Literature Review

Uranium is a naturally occurring element (a metal) that is found throughout nature, especially in granite rock. We are all exposed to it on a daily basis through the water we drink, the foods we eat and the air we breathe. Like other heavy metals, uranium can affect parts of the kidney. However, such effects only appear to occur following exposure to very high levels. Even at these levels the kidney changes are so subtle they can only be detected using very sensitive laboratory tests. Exposure for longer periods does not seem to cause greater effects. Research also suggests that the effects are reversible. Naturally occurring uranium is very slightly radioactive and international research shows no evidence that its ingestion at levels that occur naturally in the environment leads to adverse health effects relating to this aspect. In studying the health effects of uranium our focus, therefore, was on the possible chemical (metal) effects on the kidney.

The World Health Organisation currently recommends an upper level of uranium in drinking water of 15µg/L and the US Environmental Protection Agency a level of 30µg/L. It is important to note that such recommendations build in wide safety margins with levels set at many times lower than those at which any effects can be observed.

Methodology

A multi-disciplinary group from the Department of Public Health, Health Service Executive Eastern Region, the Health Service Executive South Western Area, the Department of Public Health Medicine and Epidemiology, University College Dublin and The Adelaide and Meath Hospital, Dublin incorporating The National Children's Hospital undertook the investigation.

The population of Baltinglass was classified into three groups based on the geographical distribution of the public drinking water supplies: Group A comprised those whose homes were supplied by the well in question from 1989 to 2002; Group B comprised those whose homes were supplied by the well between 1989 and 1995; Group C included the remainder of the town where the domestic water supply was never from the well. All residents in Group A and a random sample of residents from each of Groups B and C were invited to attend for screening.

Residents in the area were offered an opportunity to attend for relevant health screening at a dedicated clinic in the town. Follow-up was arranged where appropriate.

Participants completed a questionnaire in which information was sought regarding use of the relevant water supply and pertinent clinical and demographic details. Urine samples were collected and analysed for beta-2-microglobulin, retinol binding protein (indicators of proximal renal tubular dysfunction), and albumin (an indicator of glomerular function). Urinary collagen IV levels were measured as a potentially useful early marker of kidney dysfunction. Blood samples were collected from participants over the age of 10 years and were tested for urea and creatinine (an indicator of glomerular function). Urinary uranium levels were measured to estimate exposure. Height, weight and blood pressure were also recorded.

Information was communicated to the individual and their general practitioner as soon as results became available. Where further follow-up was required participants were referred to a kidney specialist.

Results

Screening commenced in July 2003 and 545 local residents from groups A, B and C were screened. The overall household response rate was 71%.

Approximately 8% of participants were referred to their general practitioners for the management of findings such as high blood pressure or suspected cystitis. The referral rate was similar in the three groups at approximately 7% in groups A and B and 11% in Group C.

The rates of referral for a nephrology opinion were also broadly similar in the three groups (at approximately 5%) being marginally lower in Group A (5%) than in groups B and C (6% and 7% respectively). A very small number of people were found to have kidney problems that were due to pre-existing conditions or kidney infections in the past. Of critical importance is that not a single case of kidney disease due to uranium exposure has been found.

No association was found between uranium exposure (whether based on area of residence or urinary uranium levels) with the indicators of kidney dysfunction.

Discussion and conclusion

Following the detection of raised uranium levels in one of the three drinking water supplies to a town in County Wicklow, a detailed public health study was carried out. This was the largest study to date in this field of research internationally, and the first such study in Ireland.

We found that the consumption of drinking water containing uranium at the levels measured in this case had no discernable effect on kidney function despite using a range of sensitive and specific tests and referral for a consultant nephrology opinion where indicated. Of particular importance we have found no person with kidney disease due to uranium exposure. In addition no effects on general health and well-being were observed. These findings are consistent with major studies worldwide.

INTRODUCTION

In 2002, raised levels of uranium were found in one of the three public drinking water supplies to the town of Baltinglass in County Wicklow. Subsequent analysis confirmed that the uranium was of natural origin and therefore came from the underlying granite rock in the area. The supply had been in use for a number of years. The supply was discontinued in November 2002.

In view of the exposure to uranium at somewhat higher than usual levels and the resulting concern of the local population and their elected representatives a public health study was undertaken.

A multi-disciplinary group from the Department of Public Health, Health Service Executive Eastern Region, the Health Service Executive South Western Area, the Department of Public Health Medicine and Epidemiology, University College Dublin and The Adelaide and Meath Hospital, Dublin incorporating the National Children's Hospital undertook the investigation to determine whether exposure to uranium had led to health effects in the local population.

Residents in the area were offered an opportunity to attend for relevant health screening at a special clinic in the town. Follow-up was arranged where appropriate.

BACKGROUND

The Environmental Protection Agency commenced a national monitoring programme of groundwater in 1995 as part of its mandate to monitor the environment.[1] The purpose of the programme was to define the state of groundwater quality and to detect any trends therein. The main concern regarding the quality of groundwater is its suitability as a source of drinking water, for use in the food processing and bottled water industries as well as in other industrial processes. Sampling was carried out twice yearly at 250 boreholes and wells on a national basis, some of which were in use as sources of drinking water. The range of metals analysed was subsequently expanded to include measurement of levels of uranium as well as several other metals. Analysis of samples taken during the course of the survey indicated that levels of uranium were generally low (below the World Health Organisation guideline level) and in many cases were below the limit of detection of less than one microgram per litre (µg/L). However, concentrations of uranium in excess of guideline levels recommended by the World Health Organisation and by the United States Environmental Protection Agency were found in some of the samples.

As part of the above survey, raised levels of uranium (initially between 120µg/L and 142µg/L) were found in one of the three wells that supplied drinking water to the town of Baltinglass, County Wicklow. The supply was discontinued and the whole town was subsequently supplied with water sourced from both the other two wells. Subsequent testing of this supply showed uranium levels to be below 2µg/L with normal radon levels. Later analysis of samples from the boreholes of the disused well confirmed that the uranium was of natural origin and that the levels had fallen to 93µg/L and 107µg/L in the two samples taken in 2004.[2]

Local authorities throughout the country were subsequently advised by the Environmental Protection Agency and the Department of the Environment, Heritage and Local Government to check for the possible presence of uranium in public and private drinking water supplies in their areas.[1]

LITERATURE REVIEW

Uranium

Uranium is a naturally occurring heavy metal that is found throughout nature. It is present in small amounts in rocks, soil, air, water, plants and animals.[3] It is present in greater amounts in some rocks such as granite, phosphate deposits and various other mineral deposits. Uranium has been detected in a variety of foodstuffs, particularly in shellfish, but also in vegetables, cereals and fish at lower levels.[4] If the amount present in rock is great enough, the uranium may be present in commercial quantities and can be mined.[5]

Given that uranium is found throughout nature we are all exposed to uranium to some extent. It is estimated that on average people take in about one to five micrograms (μg) of uranium per day in food and drink.[3] However, in areas with high levels of uranium in the underlying rock and consequently in the groundwater, higher intakes of uranium have been documented. The primary exposure pathway in that situation is direct ingestion of water, which has been shown to account for 99% of the amount of uranium ingested.[6] In such circumstances, individual intakes in the order of hundreds of micrograms per day have been recorded in parts of Canada, the United States and in Finland.[7,8,9,6]

Natural uranium exists as a mixture of three different forms (isotopes) with more than 99% of naturally occurring uranium consisting of uranium 238.[5] Uranium 234 and uranium 235 make up a small percentage of natural uranium. Like many heavy metals, natural uranium is slightly radioactive. Uranium 238 is the least radioactive of its three forms.

An industrial process called enrichment can be used to increase the amount of uranium 234 and uranium 235 present and to decrease the amount of uranium 238.[5] The product of this process is referred to as enriched uranium and the by-product is known as depleted uranium. Enriched uranium is up to 75 times more radioactive than natural uranium and is used in nuclear power reactors. Depleted uranium is a very dense metal and is used, for example, in the manufacture of airplanes and helicopters to strengthen certain critical parts.

When uranium is ingested, only a small percentage (approximately 2%) is absorbed from the gut into the bloodstream, the rest being directly excreted in the faeces.[10,11, 12] Most of the absorbed uranium is filtered out through the kidneys within days.[3] A small percentage is excreted more slowly with an estimated biological half-life (the time required for half of the substance to be eliminated from the body) of between 30 and 340 days. The kidney is considered to be the organ most sensitive to the effects of uranium.[3,4,5]

Exposure guidelines

The World Health Organisation guideline which was 9µg/L has recently been revised to a Provisional Guideline Value of 15µg/L[13]. This value is provisional due to difficulty in achieving this level in certain geographical regions and the need for more epidemiological studies. The United States Environmental Protection Agency recommends an upper level of 30µg/L[14] .

There is at present no national or European standard for uranium in drinking water. It has been recommended that limits for natural uranium in drinking water should be based on the chemical effects rather than on any hypothetical radiological effects, which has not been observed in humans or animals.[11] Hence, the calculation of minimal risk levels is based on possible changes to the kidney as it is considered to be the organ most sensitive to the effects of uranium.[5] Recommended safety limits are estimated using the daily intakes from animal experiments that produce no apparent effect on the animal kidney. These intakes are reduced by an “uncertainty factor” of 100 to take into account possible differences in the vulnerability of animals and humans to the effects of uranium, differences in the amount of uranium reaching the kidneys and possible limitations of the animal experiments.[13] Given the safety margin factored into the calculations it is likely that consumption of water containing uranium at levels well in excess of the current guideline is not harmful to humans.

Health effects of uranium

Animal studies have shown that exposure to very high doses of uranium can affect the kidneys.[3,4,5] This occurs as a result of uranium’s chemical properties as a heavy metal. However, in this regard uranium has a weaker effect than other heavy metals such as lead, cadmium or mercury.[5]

Animal studies suggest that any effects are most likely to occur in the renal tubule, although changes at the renal glomerulus have also been reported in some studies.[3,5] The extent and persistence of effects appear to be dose and species dependent. Age also appears to be a contributory factor with older animals showing increased sensitivity to the kidney effects of uranium. Following discontinuation of exposure, repair and regeneration of the lining of the kidney tubule has been observed.

Although the kidney has been identified as the organ most sensitive to the effects of uranium, possible effects of chronic ingestion of uranium on other organ systems have also been extensively studied in animal experiments. A major review concluded that exposure to uranium is unlikely to cause any effects on gastro-intestinal, cardiovascular, respiratory, neurological, haematological, endocrine or immune systems.[5] Histological changes in liver tissue have been reported in some studies following exposure of animals to very high doses of uranium. However, studies indicate that the liver is considerably less sensitive than the kidney. It has been shown that uranium can cross the placenta in animals to a very limited extent. One study estimated that less than 0.03% of an intravenous dose of uranium crossed the placenta. Effects on the animal foetus have not been observed except at doses that would be far above any plausible human exposure.[5,15]

Natural uranium is slightly radioactive and carcinogenic effects have not been observed in animal studies even after long-term ingestion of very high doses of natural uranium.[5,11] In this regard, a comprehensive review by the Committee on the Biological Effects of Ionizing Radiation concluded that "exposure to natural uranium is unlikely to be a significant health risk in the population and may well have no measurable effect".[16] A recent review by the International Agency for Research on Cancer stated that there is not adequate evidence in humans to determine the carcinogenicity, if any, of natural uranium.[17] It has been estimated that water supplies with levels of uranium in the region of 100-140µg/L would provide only a small fraction of the average dose of radiation received annually by persons from all sources of radioactivity, including natural background sources such as cosmic rays and radon gas, as well as medical, occupational and other sources.[2]

A review of epidemiological studies carried out on workers occupationally exposed to very high levels of uranium, such as uranium miners and mill workers, concluded that they showed fewer than expected total deaths from neoplasms of the kidney as compared with the mortality rates for these conditions in the general population, fewer than expected total deaths from genitourinary disease and fewer than expected total deaths from chronic kidney failure.[15] A separate study on the kidney function of uranium mill workers chronically exposed to very high levels of inhaled uranium did suggest an association between exposure and kidney tubular dysfunction, with increased urinary excretion of beta-2-microglobulin and aminoacids.[18]

Drinking water studies

The presence of high levels of uranium in drinking water sources has been found in many parts of the world including Canada, Scandinavia and the United States.[7,19,8,9] Several studies have been conducted into the health effects in populations exposed to uranium in their drinking water to ascertain at what levels kidney effects might occur and to determine their nature.

Following a pilot study by Mao et al in 1995[19] the kidney effects of chronic ingestion of uranium in drinking water were studied by Zamora et al in Nova Scotia, Canada in 1998.[7] Participants were recruited from residents of a village in Nova Scotia based on uranium levels in their well water. A further group of healthy subjects, matched by age and gender to the first group were selected from a pool of volunteers residing in Ottawa, Ontario, which was supplied by surface water with uranium concentrations of less than 1µg/L. In total there were 50 eligible participants, and these were re-classified into a low exposure group (20 persons), whose drinking water contained less than 1µg/L of uranium, and a high exposure group (30 persons), whose water contained uranium at levels that ranged from 2µg/L to 781µg/L of uranium. Approximately half of the subjects in the high exposure group consumed water with uranium levels above 100µg/L. The duration of exposure ranged from 1 to 59 years in the study population. A number of indicators of kidney function were measured including glucose, beta-2-microglobulin, creatinine and protein. Markers of cell effects were also measured including alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase and N-acetyl-ß-D-glucosaminidase. A correlation was found between uranium intake and two markers of tubular dysfunction, namely beta-2-microglobulin and urinary glucose. The level of uranium exposure did not affect creatinine and protein, indicators of glomerular injury. The authors concluded that long-term ingestion of uranium by humans may produce subclinical interference with proximal tubular kidney function at markedly elevated levels of uranium found in some groundwater supplies.

A subsequent large study conducted in 2002 by Kurttio et al in southern Finland examined kidney effects in a population who had been exposed to high levels of uranium in water from drilled wells.(8) The study population consisted of 325 persons. Uranium levels in the 194 wells ranged from 0.001µg/l to 1,920µg/l with a mean of 131µg/L and duration of exposure varied from 1 to 34 years. Urinary uranium levels ranged from 1µg/L to 5,650µg/L with a mean of 424µg/L. Excretion of glucose, calcium, phosphate and beta-2-microglobulin were selected as indicators of effects on the proximal tubule, whilst creatinine clearance and urinary albumin were measured as indicators of glomerular function. An association between uranium exposure and increasing fractional excretion of calcium and phosphate was demonstrated. However, this effect only became statistically significant at drinking water levels of 300µg/L or higher and the results remained within the normal physiological ranges for these parameters even in those persons exposed to very high levels of uranium. No association between uranium exposure and excretion of beta-2-microglobulin was demonstrated, nor was there any correlation found between the duration of well-water use or the cumulative uranium intake and kidney test results. The authors concluded that uranium exposure is weakly associated with altered kidney tubular function and that effects are not likely to increase with increasing duration of exposure.

In 2004 Orloff et al published a study conducted in South Carolina, USA where high concentrations of uranium had been detected in water samples taken from private wells in a residential community.(9) A total of 105 participants from 35 households took part in the study. The concentration of uranium in drinking water ranged from 1.8 to 7780µg/L with a mean value of 620µg/L and the median concentration was 157µg/L. Exposure duration ranged from one to 20 years. Elevated concentrations of uranium were detected in urine samples collected from residents, with a mean of 0.40µg/g creatinine (equivalent to 188pmol/mmol) two months post discontinuation of exposure and 0.27µg/g creatinine (equivalent to 127pmol/mmol) in urine samples collected eight months after exposure had ceased. Although urine levels were found to have decreased on average by 78% in subjects with the highest initial levels, 87% of urine uranium concentrations remained above the normal levels of a reference population at the second round of testing (eight to ten months post-exposure). The authors concluded that urinary uranium concentrations were correlated with uranium concentrations in water supplies, but were not associated with duration of consumption or participant age. Retinol binding protein levels were measured as a marker of proximal tubular dysfunction at approximately eight months post-discontinuation of exposure. Only a few of these (three out of 79) were raised and on re-testing were found to be normal.(20)

In the United States, a large study of the general population has documented urinary uranium levels ranging from below the limit of detection to above 0.046µg/L.(21) In the Third National Health and Nutrition Examination Survey of the United States general population, age and racial group appeared to influence urinary uranium levels with slightly higher levels detected in children than in older groups and higher levels found in Mexican Americans than in other ethnic groups.

Selection of biomarkers of renal injury

Biomarkers are defined as indicators signalling events in biological systems or samples.(5) A biomarker of exposure is a substance that is foreign to the body that is measured within a compartment of an organism. It could also be the breakdown products of that substance or the product of the interaction of that substance with target molecules or cells. Biomarkers of effect are defined as any measurable biochemical, physiological, or other alteration within an organism that can be recognized as an established or potential health impairment or disease. These markers are not usually substance specific.

Biomarkers of exposure to uranium include the chemical or radiological detection of uranium in the urine. Inductively coupled plasma mass spectrometry is one of the most sensitive and accurate techniques for the quantification of uranium isotopes.(5)

The ideal urine sample is a 24-hour collection. However, researchers in this area have recommended that spot urine samples can be used if the uranium concentration is expressed as a ratio to urinary creatinine.(23) A recent study of exposed Gulf War veterans found a high correlation between creatinine standardised uranium levels in spot urine samples and levels measured in 24 hour creatinine standardised collections, substantiating the utility of spot urine samples for the determination of urinary uranium.(24)

Biomarkers of effect were selected to detect the potential effect of uranium on the kidney.(5) A minimal battery of tests has been developed to assess subclinical kidney effects in the epidemiological setting.(22) Most of the biomarkers recommended by the Agency for Toxic Substances and Disease Registry are analytes measured in urine. As these can be affected by the state of hydration it is necessary to standardise the results for urinary concentration by expressing them as a ratio to urinary creatinine.

The inclusion of serum urea and creatinine is recommended as they are routine diagnostic tests. However, these parameters have certain limitations in that they lack sensitivity, and they may be influenced by other variables. For example serum urea levels are influenced by protein intake and tissue catabolism, whilst serum creatinine is related to age, sex and muscle mass.(25)

Further tests were advised to reflect the function of different parts of the nephron. Beta-2-microglobulin is used in the evaluation of substances believed to affect the proximal renal tubule.(22) It is a low molecular weight protein that is filtered at the glomerulus and reabsorbed by the cells of the proximal renal tubule. Several studies have shown a correlation between levels of beta-2-microglobulin and uranium exposure.(7,18) Retinol binding protein is a similar protein, now more widely used to detect tubular dysfunction due to its greater reliability and stability in acidic urine.(22) Urinary albumin levels can provide an early indication of injury to the glomerulus, but exercise can increase the urinary excretion of proteins and thereby increase urine levels of this biomarker in some individuals.

Collagen IV is a protein found in the basement membrane of the nephron that is currently being considered as a potentially useful early indicator of nephropathy particularly in diabetes.[26,27,28] Raised levels have also been described in non-diabetic chronic kidney disease[26,29,30] and it is likely that raised levels can reflect a variety of pathological processes or indeed normal physiological changes. For example, diurnal variation in collagen IV levels has been demonstrated, with higher mean levels in random urine samples as compared with morning urine samples.[31] It is important that this aspect be considered in the interpretation of collagen IV levels measured in spot urine samples.

In drawing up an appropriate series of biomarkers it is necessary to consider the relative and combined value of the tests in terms of sensitivity, specificity and positive predictive value. It is also important to consider the logistical implications as regards sample collection, storage and transportation, which can be complex when large field studies are being conducted. These considerations influence the final selection of biomarkers for use in a given study. Timed urine collections, such as 24 hour collections, although ideal from a scientific perspective, can pose practical problems even in the most controlled clinical environment.[22] Furthermore, the collection of blood samples is somewhat less acceptable to the public than the collection of urine samples.

Prevalence of kidney disease

There is no information on the prevalence of kidney disease in the community in Ireland. The prevalence of chronic kidney disease in the United States adult population has been estimated based on the results of a large population survey and using standardised criteria.[32] A nationally representative sample of 15,625 adults from the Third National Health and Nutrition Examination Survey was analysed. The prevalence of chronic kidney disease in the US adult population was 11%. This comprised 3.3% of individuals with stage 1, defined as persistent albuminuria with a normal glomerular filtration rate, 3% had stage 2 disease, defined as persistent albuminuria with a glomerular filtration rate of 60 to 89 ml/min/1.73m2, 4.3% had stage 3 with a glomerular filtration rate of 30 to 59ml/min/1.73m2, 0.2% had stage 4 disease with a glomerular filtration rate of 15 to 29ml/min/1.73m2 and 0.2% had stage 5, or kidney failure. Key predictors of chronic kidney disease included age, gender, hypertension and diabetes.

Demographic and Health profile of Baltinglass

Information from the 2002 census was used to describe the demographic profile of Baltinglass town.[33] The population of Baltinglass was noted in the census at 1,963 persons. Of these, 967 were male and 996 were female, giving a male to female ratio of 49 to 51. Twenty four percent of residents were aged less than 15 years, with 27% aged between 15 and 34 years, 26% aged between 35 and 54 years, 13% aged between 55 and 69 years and 10% aged over 70 years.

Cancer incidence data provided by the National Cancer Registry for the Eastern Region[34] was geocoded by electoral division by the Health Information Unit, Department of Public Health, Health Service Executive Eastern Region. It is reassuring to note that based on 1994 to 2000 data the standardised incidence of cancer was significantly lower in Baltinglass than in the Eastern Region. The incidence of individual cancer types including lung, colorectal, breast, prostate, bone and kidney cancer were all similar to that of the Region.

METHODS

Study design

Baltinglass town is situated in the southern tip of County Wicklow and until November 2002 the public drinking water supply had come from three separate wells at Parkmore, Tenorin and Lathaleere. Following consultation with staff from the Environmental and Sanitary Services section of the local authority the water distribution zones of the town were mapped by the Health Information Unit, Department of Public Health, Health Service Executive Eastern Region using geographical information system technology (see appendix 1).

A cross-sectional survey approach was adopted. The population of Baltinglass was divided into three groups based on the geographical distribution of the public drinking water supplies: Group A comprised those whose homes were supplied by the well in question from 1989 to 2002; Group B comprised those whose homes were supplied by this well between 1989 and 1995; Group C included the remainder of the town where the domestic water supply was never from the well.

All residents in Group A (143 households) were invited to participate in the study and a random sample of residents from groups B and C (75 households from each) were also invited to participate to act as comparison groups.

It was considered that this study design would give approximately 300 participants in Group A and approximately 100 in each comparison group, and that such numbers would provide adequate statistical power for appropriate intergroup comparisons to be made. It was estimated that a study population of 300 would provide adequate statistical power ($\alpha = 0.05$ one-sided, $1-\beta = 0.9$) to detect a 20% increase in β-2-microglobulin excretion and creatinine clearance.

Study populations

The Register of Electors formed the sampling frame for the selection of households for invitation to participate.[35] Registered voters in the Baltinglass electoral division were grouped into households and classified by address into groups A, B and C with the assistance of local authority staff familiar with the area and the water supply zones.

Households whose domestic water was supplied by a private well or who had moved into the area since the supply was discontinued were excluded from the study. Long stay patients at Baltinglass District Hospital were excluded as this was an elderly group of patients in which one would expect to find renal problems and that would be regularly reviewed by their general practitioner. It would have been inappropriate to put such patients through a series of investigations.

A number of people were screened who worked in the local area or on an opportunistic basis. Whilst these were not included in the overall analyses as they were not within the criteria for the study groups, it is important to note that no case of renal disease attributable to uranium exposure was identified among these.

Data collection

Participants completed a questionnaire in which information was sought regarding exposure to the relevant water supply and pertinent clinical and demographic details. In addition, the Short Form-12 questionnaire was used as a measure of general health and well being.[36] Urine samples were collected and analysed for beta-2-microglobulin and retinol binding protein (indicators of proximal renal tubular dysfunction), and albumin (an indicator of glomerular function). Urinary collagen IV levels were measured as a potentially useful early marker of kidney dysfunction. Blood samples were collected from participants over the age of ten years and were tested for urea and creatinine (an indicator of glomerular function). To estimate exposure, urinary uranium levels were also measured. The height, weight and blood pressure of each participant were recorded.

Information governance

The study was submitted to and discussed with the chairperson of the Ethics Committee of the Faculty of Public Health Medicine, Royal College of Physicians of Ireland. In view of the increased exposure to uranium and the resulting concern of the local population and their elected public representatives the study was deemed to be necessary from a service perspective. Hence, formal ethical approval for the study was not considered to be indicated.

All data collected during the study was treated in strictest confidence. Personal details such as names and addresses were not included on any database. To ensure confidentiality and privacy, any data resulting from the study is presented in aggregate form and not on an identifiable basis.

Questionnaire design

The questionnaire was developed specifically for the purposes of the screening study and piloted prior to its use in the field. Certain questions were based on those used by Kurttio et al in the Finnish study with the permission of the authors[37].

Topics covered by the questionnaire included the following: demographic details; residential history; occupational history with particular reference to potentially nephrotoxic exposures; food and water intake including the source of the water; medical history and medications; tobacco and alcohol consumption; general health and well-being; level of concern. Participants were invited to add any additional comments as they saw fit.

Pilot study

The questionnaire was piloted in April 2003 with approximately 30 individuals who were not included in the final study groups. Modifications were made where required to improve clarity, flow and appropriateness of questions.

Staffing

The Department of Public Health, Health Service Executive Eastern Region, on behalf of the Health Service Executive South Western Area, established a Scientific Steering Group consisting of personnel from the Department, the Health Board, the Department of Public Health Medicine and Epidemiology (University College Dublin) and Consultants from both the Department of Renal Medicine and the Department of Clinical Chemistry, The Adelaide and Meath Hospital, Dublin incorporating The National Children's Hospital.

A Project Manager, two research nurses and a clerical officer were recruited for the duration of the project.

A subgroup of the Steering Committee met on a regular basis to review sets of clinical and laboratory results as they became available. It was the function of this group to interpret the clinical results and to recommend the appropriate follow up for each person.

Communications

The study was extensively advertised locally in order to ensure the highest possible participation rate. Information regarding the study was submitted to local print media and to the parish bulletin. Notices were displayed in prominent locations around the town including supermarkets, banks, doctors' surgeries, the local post office and the local health centre.

Meetings were held with local community representatives at the outset and when the study was underway representatives were kept informed as to progress. Key persons within the community such as general practitioners and public health nurses were briefed as to the nature and purpose of the study.

Screening clinic

A special screening clinic was established at Baltinglass District Hospital. The necessary equipment was ordered and put in place.

From the outset the clinics were appointment based. In addition "out of hours" appointments were offered to meet the needs of the local population. Clinics were held from 10am to 4pm three days of the week and from 10am to 8pm on two days of the week. Screening commenced on July 2003 and continued until November 2003.

Invitations

Household invitation letters and information sheets were sent to all households included in the study on a phased basis. Priority was given to residents in Group A.

Householders were invited to contact the clinic secretary who scheduled suitable appointments for the household. Staff facilitated any requests for evening appointments. If no response was received following the first invitation letter two reminder letters were sent to each household. Door to door calls were also made to 64 households who had not responded. Persons who failed to attend their appointment were contacted and an alternative appointment was arranged if required.

Health screening

On arrival at the clinic participants were greeted by the receptionist who recorded their details (names, date of birth, household address).

A member of the team explained the screening process involved and answered any questions posed. The participants (or the parent/guardian of those under 16years) were asked to sign a form giving their consent to take part in the study.

The participant was given a urine collection container and asked to provide a urine sample. In the case of infants, parents were supplied in advance with urine bags and were asked to collect a fresh morning sample from their child prior to attending the clinic. Dipstick analysis was carried out using urine multi-test dipsticks and the results read by a Dipstick Scanner.[(38)] The urine samples were pipetted into prepared containers for each test in accordance with laboratory instructions. Containers were then sealed and stored in a fridge reserved for this study.

Height was measured in accordance with standard procedures using a wall mounted height measure.[(39)] Weight was measured using a digital scales.[(40)] These were recorded on the clinic report form.

The participant was asked to complete an interviewer-administered questionnaire. In general interviews were conducted on a one to one basis. When appropriate some respondents were interviewed in groups for example parents with young children.

Blood pressure was measured for participants aged ten years and over.[(41)] A blood sample was taken from participants who were aged over ten years. Research staff had been trained in phlebotomy techniques and procedures at the Department of

Phlebotomy in The Adelaide and Meath Hospital, Dublin incorporating The National Children's Hospital. In the case of persons who did not wish to undergo phlebotomy, urine samples were collected, they underwent the remainder of the screening procedure and were included in the study.

Participants were thanked for participating and informed that a report of their clinical outcome would be sent to their general practitioner in due course.

Clinic report form

A standard clinic report form was completed for each client who attended the screening clinic. This form served as an ongoing clinical record for each participant. If a client was referred to their general practitioner for follow-up of an incidental finding a copy of the clinic report form was sent to the general practitioner along with relevant reports (e.g. urine results).

Transport of samples

A medical courier service was employed for the duration of the study to transport the samples to the laboratory.

Selection of biomarkers

Most of the biomarkers recommended by the Agency for Toxic Substances and Disease Registry to detect the effects of heavy metals are substances measured in urine.(22) For substances measured on spot urine samples it is necessary to standardise the results for urinary concentration by expressing them as a ratio with urinary creatinine to account for the state of hydration. Exercise is known to increase urinary excretion of proteins and can affect the levels of those biomarkers that are proteins.

The urinary levels of beta-2-microglobulin and retinol binding protein were used to detect renal tubular dysfunction.(42) Serum urea and creatinine were measured(43,44) as routine diagnostic tests of kidney function but they lack sensitivity and can be influenced by other factors. Serum urea is affected by protein intake and tissue catabolism whilst serum creatinine is related to age, sex and muscle mass but is considered a useful marker of significant glomerular pathology.(25) Urinary excretion of albumin was measured(42) as an early indicator of glomerular injury.(22) Urinary uranium levels were measured as a marker of exposure to uranium using inductively coupled plasma mass spectrometry.[45]

Collagen IV is a protein currently being considered as an early indicator of nephropathy, and was included in our study as a potential marker. Given the absence of reference ranges for urinary collagen IV in Caucasian populations The Adelaide and Meath Hospital, Dublin incorporating The National Children's Hospital undertook an additional separate study of children not involved in the Baltinglass study to determine the reference range of collagen IV in Irish children. Ethical approval was obtained for the study and informed consent was given by the parents/guardians of all children involved. In total, 41 children attending the paediatric outpatient department for non-kidney conditions were recruited to the study. A random urine sample was obtained from each participant. The collagen IV and creatinine levels of each sample were measured and the results expressed as the ratio of urinary collagen IV to creatinine.[46,47] The biological variation of collagen IV in healthy adults was also studied. Random urine samples were collected over a number of days from each of seven healthy adult volunteers (again participants were not involved in the Baltinglass study) and the urinary collagen IV/creatinine level of each sample was measured for the purpose of determining whether there was variation over short time periods.

Client feedback and referral

Clients were advised by the nurse or doctor to attend their general practitioner for further follow-up where indicated, for example if the blood pressure was high or if cystitis was suspected.

Laboratory results were reviewed by the clinical subgroup as they became available and appropriate follow-up was recommended where necessary. If repeat urine samples were requested the client was asked to give a morning sample if possible, so as to minimise the possibility of exercise related proteinuria which is of particular relevance to collagen IV and albumin measurement. Where referral for specialist opinion was advised, the Project Manager discussed this directly with the client and also arranged the referral. The clinical work-up of those referred for specialist opinion included a kidney ultrasound, a 24-hour urine collection and relevant blood tests.

Statistical analyses

The Irish Social Class Scale was used to classify occupational groups. Epi Info version 6 was used for data entry.[48] Anonymous clinical data was entered separately using Excel and subsequently linked to the laboratory data. All statistical analyses were performed using Epi Info and R.[49] Linear regression was used to examine association between continuous variables. Robust regression as implemented in the MASS library in R was used to check results from linear regression models. One-way analysis of variance and the Kruskal-Wallis rank sum test, were used to compare means between the three groups. Chi-squared analysis for trend was used to compare prevalences in the three study groups. Adjustment for clustering at houshold level was done using the nlme procedure in R.

Data from the Short Form-12 questionnaire was analysed using the software package SAS[50] and Irish regression weights.[36] Significance testing was carried out using the Kruskal-Wallis rank sum test as appropriate. For all statistical tests, a probability of $p<0.05$ was considered statistically significant and such p values are marked with an asterisk (*) in the results section.

RESULTS

RESPONSE RATES

Screening commenced in July 2003. The main study population consisted of 545 individuals: 326 in Group A, 122 in Group B and 97 in Group C.

As shown in table 1, household response rates in groups A, B and C were 77%, 67% and 62% respectively.

Table 1: Household response rates

Group	Households invited	Households attended (%)	Persons attended
Group A	143	110 (77%)	326
Group B	75	50 (67%)	122
Group C	73	45 (62%)	97
Total	291	205 (71%)	545

X^2=6.1, degrees of freedom (df)=2, p=0.05*

Seven subjects were excluded because their domestic water was supplied by private wells the uranium levels of which were not known. A further six subjects presented for screening initially but chose not to complete the screening process.

DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

Gender and age

The male to female ratio of the study population was 46 to 54 and the gender balance was similar in each of the study groups. Of the three study groups, Group A had a significantly younger population as shown in table 2. The mean age of participants in Group A was 29 years as compared to 39 and 42 years in groups B and C respectively (p<0.001*). In Group A 63% of people were under 35 years of age and 13% were aged 55 years and over, whereas in Group C the equivalent figures were 37% aged less than 35 years and 39% aged 55 years and over.

Table 2: Study population by age-group

Group	<16 years	16-34 years	35-54 years	55-69 years	70+ years
Group A	116 (36%)	88 (27%)	80 (24%)	31 (10%)	11 (3%)
Group B	29 (24%)	22 (18%)	33 (27%)	23 (19%)	15 (12%)
Group C	21 (22%)	15 (15%)	23 (24%)	27 (28%)	11 (11%)
All	166 (30%)	125 (23%)	136 (25%)	81 (15%)	37 (7%)

X^2 = 45.9, df=8, p<0.001*

Social class

Group B had the highest proportion of people in social classes 5 and 6 at 33%, compared to 25% and 17% in groups A and C respectively (see table 3) but this difference was not statistically significant.

Table 3: Study population by social class (SC)

Group	SC 1&2	SC 3&4	SC 5&6	Total
Group A	103 (35%)	114 (40%)	74 (25%)	291
Group B	37 (34%)	35 (33%)	36 (33%)	108
Group C	29 (33%)	44 (50%)	15 (17%)	88
All	169 (35%)	193 (40%)	125 (25%)	488#

X^2 =8.95, df=4, p=0.06

#Social class not available on 58 persons

Smoking

The proportion of adults who reported having ever been a smoker and the mean duration of smoking was similar in the three groups as shown in table 4. The average cumulative intake of cigarettes was highest in Group B.

Table 4: Study population and smoking (age 16 years+)

Group	Ever smoked n (%)	Years smoked (mean)	Cumulative intake cigarettes (mean)	Total
Group A	110 (52%)	9.5	53,824	210
Group B	45 (48%)	10.3	73,308	93
Group C	37 (49%)	11.8	70,646	76
Total	192 (51%)	10.1	61,979	379

For percentage who ever smoked: X^2 = 0.4, df=2, p=0.8
For duration of smoking: F stat=0.7 p=0.5

Medical risk factors for kidney disease

The prevalence of well-known medical risk factors for kidney disease, including hypertension, diabetes and a family history of kidney disease was examined for each study group. As demonstrated in table 5, Group B had a higher prevalence of hypertension. The prevalence of diabetes and the proportion of persons who reported a family history of kidney disease were similar in the three groups.

Table 5: Prevalence of kidney risk factors (age 16 years+)

	Hypertension n (%)	Diabetes n (%)	Family history n (%)	Total
Group A	20 (10%)	3 (1%)	20 (10%)	210
Group B	20 (22%)	5 (5%)	8 (9%)	93
Group C	14 (18%)	3 (4%)	3 (4%)	76
All	54 (14%)	11 (3%)	31 (8%)	379
X^2 df p-value	8.0 2 0.02*	5.0 2 0.07	2.7 2 0.3	

Occupational and leisure exposure to heavy metals

When asked about specific occupations that could involve exposure to heavy metals, a small number of respondents in each group had worked in these occupations. In total, 12 adults had worked in welding, five in the chemical industry; five as sheet metal workers; two had worked at nickel plating or in a finishing plant; two as a dentist or dental nurse and one person had worked in melting of metals. No participants had worked in a battery or accumulator factory. As shown in table 6, occupational and leisure exposure was similar in the three groups.

Table 6: Occupational and leisure exposure to heavy metals (age 16 years+)

	Ever exposed	Persons exposed >1 year	Metal work as hobby	Total
Group A	17 (8%)	12 (6%)	7 (3%)	210
Group B	8 (9%)	5 (5%)	5 (5%)	93
Group C	4 (5%)	3 (4%)	0 (0%)	76
All	29 (8%)	20 (5%)	12 (3%)	379
X^2 df p-value	0.8 2 0.7	0.5 2 0.7	4.3 2 0.1	

EXPOSURE TO THE WATER SUPPLY

Duration of exposure

Duration of exposure was calculated from the reported duration of residence in the water supply zones while the relevant supply was in use. The maximum possible duration of exposure was 12.9 years in Group A and 5.7 years in Group B. Mean duration of exposure was highest in Group A and this was statistically significant (see table 7).

Table 7: Duration of exposure

	Duration of exposure in years			<1 year	1-6 years	>6 years
	Mean	Median	Range	n (%)	n (%)	n (%)
Group A	6.6	5.7	0-12.9	22 (7%)	143 (44%)	161 (49%)
Group B	3.7	5.7	0-5.7	32 (26%)	90 (74%)	0 (0%)
Group C	0.1	0	0-12	91 (94%)	6 (6%)	0 (0%)
Total	1.4	3.5	0-12	145 (27%)	239 (44%)	161 (29%)

F stat=114, p<0.001* X^2 = 377, df=4, p<0.001*

Water consumption

The percentage of participants who reported that "more than half" or "all" of their water intake was from their home water supply was 84%. The proportion who reported that their entire water intake was from their home supply was 65% as shown in table 8.

Table 8: Proportion of recent water intake (within previous year) from home supply

Group	Less than half n (%)	About half n (%)	More than half n (%)	All water n (%)	Total n (%)
Group A	21 (6%)	33 (10%)	67 (21%)	204 (63%)	325# (100%)
Group B	11 (9%)	5 (4%)	21 (17%)	85 (70%)	122 (100%)
Group C	5 (5%)	11 (11%)	18 (19%)	63 (65%)	97 (100%)
Total	37 (7%)	49 (9%)	106 (19%)	352 (65%)	544# (100%)

X^2 =6.83, df=6, p=0.3

#Question not applicable to one participant

Only a small percentage of respondents reported that they had consumed any water from supply A in places other than at home (see table 9). The percentage of adults who reported that they had consumed any water from the relevant supply at work was 5% and just 3% of respondents stated that they had consumed this water in other locations such as in a relative or friend's house.

Table 9: Percentage of respondents who drank water from supply A within the previous year

Group	Home intake n (%)	Work intake (adults) n (%)	Other places n (%)	Any intake n (%)	Total
Group A	325 (100%)	14 (5%)	15 (5%)	325 (100%)	325#
Group B	0 (0%)	8 (8%)	1 (1%)	9 (7%)	122
Group C	0 (0%)	3 (4%)	0 (0%)	3 (3%)	97
Total	325 (60%)	25 (5%)	16 (3%)	337 (62%)	544#
X^2	544	1.3	8.7	496	
df	2	2	2	2	
p-value	<0.001*	0.5	0.01*	<0.001*	

#Question not applicable to one participant

Work intake refers to adults only and for that question %=% of adults.

As shown in table 10, over 90% of subjects in Group A had consumed 500ml or more of water from supply A per day. In contrast very few of the subjects in groups B or C had consumed such quantities of water from that supply. Only seven percent of respondents in Group B and three percent of those in Group C had consumed any (100ml or more) of the water daily.

Table 10: Total daily intake of the water (litres/day)

Group	0-99ml n (%)	100-499ml n (%)	500-1499ml n (%)	1500-2499ml n (%)	>2500ml n (%)	Total
Group A	5 (1%)	16 (5%)	87 (27%)	91 (28%)	126 (39%)	325#
Group B	113 (93%)	2 (1.5%)	5 (4%)	2 (1.5%)	0 (0%)	122
Group C	94 (97%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)	97
Total	212 (39%)	18 (3%)	93 (17%)	94 (18%)	127 (23%)	544#

#Question not applicable to one participant

X^2 =478, df=8, p<0.001*

CLINICAL OUTCOMES

Twenty nine persons out of a total of 545 were referred to a consultant nephrologist for investigation of abnormal screening tests. Of these, 14 were referred due to raised serum creatinine, six due to microalbuminuria, one person was referred due to raised creatinine with microalbuminuria, six due to raised urinary collagen IV levels and two were referred because the excretion of both urinary collagen IV and urinary albumin were raised.

The rate of referral was similar in the three groups, being lowest in Group A at 5% as compared to 6% and 7% in groups B and C respectively (see table 11). The proportion of subjects with normal kidney screening test results was highest in Group A at 93%, and lowest in Group B at 85%. Participants found to have abnormal kidney test results consistent with their known medical history (17) or advanced age (5) were referred to their general practitioner for ongoing care.

Table 11: Screening outcomes by study group

	Normal n (%)	Known kidney disease n (%)	Referred for specialist opinion n (%)	Total
Group A	303 (93%)	8 (2%)	15 (5%)	326
Group B	104 (85%)	11 (9%)	7 (6%)	122
Group C	86 (89%)	4 (4%)	7 (7%)	97
Total	493 (91%)	23 (4%)	29 (5%)	545

For referral rate: X^2=0.78, df=2, p=0.7

No case of kidney disease attributable to uranium exposure has been identified. Of the 29 participants who were referred for specialist opinion, three have been found with kidney problems due to pre-existing conditions or kidney infections in the past.

Repeat urine samples were requested from 84 participants (15%) for repeat clinical testing as follows: 19 were done for repeat urinary collagen IV; 30 for repeat urinary albumin; 4 for repeat of both albumin and collagen IV levels and the remainder for repeat dipstick and/or mid-stream urine for culture and sensitivity. Whilst not statistically significant ($X^2=4$, df=2, p=0.14) the rate of repeat clinical testing of urine was lowest in Group A (13%) as compared to Group B (19%) and Group C (20%). Repeat analysis of exposure markers was carried out on 22 samples. Repeat serum creatinine was carried out on one client due to an initial borderline result.

Other clinical findings

Participants with incidental findings found at screening such as a high blood pressure reading (23 persons) or an abnormal urinary dipstick result with normal kidney laboratory tests (18 persons) were advised by the screening team to attend their general practitioner for follow-up. The rate of referral to general practitioners was similar in the three groups being marginally lower in groups A and B (7% in both groups) than in Group C (11%). This was not statistically significant.

The prevalence of irritable bowel syndrome was similar in the three areas with 0.6% in Group A (three persons), 0% in Group B and 1% in Group C (one person).

RESULTS OF KIDNEY SCREENING

Analysis was conducted on all participants from the three study groups and also following the exclusion of persons with known or strong predisposition to kidney disease. In this context the term “persons with known kidney dysfunction” refers to those with a history of significant kidney disease such as congenital disease, kidney transplantation, obstructive nephropathy or long-term diabetes.

Beta-2-microglobulin

The proportion of detectable beta-2-microglobulin was similar in all three groups both on analysis of all results and following exclusion of persons with known kidney dysfunction (p=0.5).

The ratio of beta-2-microglobulin to urinary creatinine was calculated. Where beta-2-microglobulin was less than the limit of detection, a value of half the limit of detection was assumed. No results were above the reference range maximum value of 25µg/mmol. The mean ratio was similar in all three groups both on analysis of all results and following exclusion of persons with known kidney dysfunction (see table 12).

Table 12: Beta-2-microglobulin/urinary creatinine (µg/mmol)

Group	All results Mean (median)
Group A	0.021 (0.012)
Group B	0.051 (0.012)
Group C	0.02 (0.012)
Total	0.03 (0.012)

F stat=1.9, p=0.16

Retinol binding protein

Detectable levels of retinol binding protein were similar in all three groups with only one case in each group as shown in table 13.

Table 13: Retinol binding protein

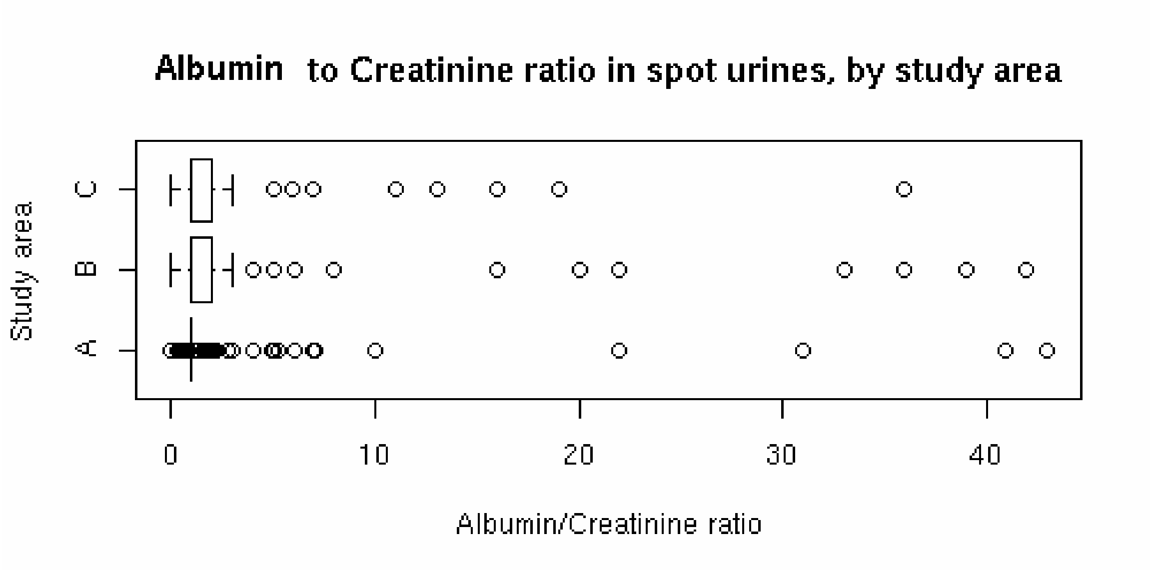
Group	Not detectable (<0.01µg/L)	Detectable
Group A	325 (99.7%)	1 (0.3%)
Group B	120 (99%)	1 (1%)
Group C	96 (99%)	1 (1%)
Total	541	3

X^2 =0.93, Degrees of freedom=2, p=0.6

The ratio of retinol binding protein to urinary creatinine was calculated. Where retinol binding protein was less than the limit of detection a value of half the limit of detection was assumed. No results were above the reference limit of 15µg/mmol creatinine. There was no difference between the mean ratio, which was 0.001 in all three groups both on analysis of all results and following exclusion of persons with known kidney dysfunction.

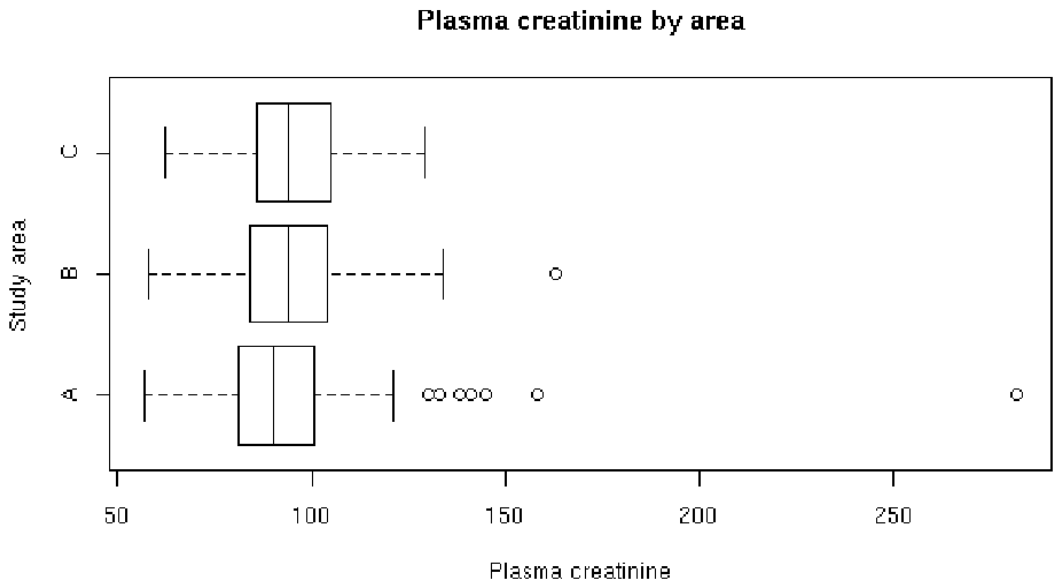
Albumin

As shown below the median albumin/creatinine ratio was similar in all three groups at 1mg/mmol both on analysis of all results and following exclusion of persons with known kidney dysfunction. A maximum reference value of 3.5mg/mmol was used for this parameter in accordance with the reference range recommended by the laboratory.



Plasma creatinine

As shown below the median plasma creatinine was similar in all three groups both when all results were analysed and on exclusion of subjects with known kidney dysfunction. A maximum reference value of 115mmol/L was used for this parameter in accordance with the reference range recommended by the laboratory.



Collagen IV

A reference range maximum value was calculated based on the results of the unexposed study population (Group C), taking the mean value plus twice the standard deviation. For adults this gave a maximum value of 6.5µg/g. A paediatric maximum value of 11.6µg/g was calculated and this was corroborated by the results of the paediatric reference range study. In Group A 13 persons were found to have raised collagen IV levels, of which eight were normal on repeat testing. Of the remaining five, three had diabetes, one had chronic kidney disease of genetic origin and one had a raised collagen IV level on repeat testing and was referred for investigation.

In Group B a similar pattern emerged with 11 persons having raised collagen IV levels, five of which were normal on repeat testing. Of the remaining six, three were attributable to significant medical conditions and three were referred for further investigation.

In Group C, four persons had raised collagen IV levels and two of these were normal on repeat testing. The remaining two persons were referred for investigation.

The results of the study to determine a paediatric reference range for collagen IV showed that the mean collagen IV/creatinine ratio of the study population was 4.74µg/g with a standard deviation of 3.34µg/g. The mean ratio was higher in males (5.89µg/g) than in females (3.64µg/g) and this was statistically significant (F-statistic=5.16, p=0.03*). Taking a maximum reference value of the study population mean plus twice the standard deviation, a maximum value of 11.4µg/g was calculated for collagen IV/creatinine levels in the paediatric population.

Assessment of the assay precision showed that the intra-assay precision was satisfactory, with a coefficient of variation obtained for each control of 4.8% to 7.3%, which was less than the coefficient of variation of 12.5% quoted by the manufacturer. However, the inter-assay precision was less satisfactory with coefficients of variation of 17.9% to 23.3% observed.

Examination of intra-day collagen IV/creatinine in healthy adult volunteers indicated that there was variation within individuals but there did not appear to be a general trend in this variation. Inter-day analysis of collagen IV/creatinine observed over five days in the same group demonstrated the presence of variation within and between individuals, but with no apparent trend.

Exposure estimates

The dose of uranium was estimated based on reported water intake as discussed above and this estimate was found to correlate strongly with levels of uranium measured in urine (p<0.001).

In the overall study population 84% of urinary uranium/creatinine levels were below the reference value for an unexposed population (24pmol/mmol creatinine). The mean level of those living in the area recently supplied by the well was 25pmol/mmol creatinine. Repeat measurement of urinary uranium/creatinine ratio was carried out approximately nine to twelve months later on a sample of those with higher levels on initial testing. This showed an overall reduction in levels of 50% and an even greater decrease of 76% in those with higher initial levels.

Regression analysis was used to detect any association between estimated uranium dose or urinary uranium levels and the established markers of kidney dysfunction including beta-2-microglobulin/creatinine; retinol binding protein/creatinine; albumin/creatinine and plasma creatinine. No significant associations were found even after duration of exposure was included in the analysis.

GENERAL HEALTH AND WELL-BEING

The mean Short Form-12 Physical Component Score and Mental Component Scores were calculated for each of the study groups using Irish regression weights.[36] There was no significant difference between the mean Physical or Mental Component Scores of the three study groups.

PERCEPTIONS OF DRINKING WATER QUALITY

The overall level of concern about water quality was highest in Group A with 47% reporting that they were quite or very concerned as compared to 34% and 32% of groups B and C respectively.

Forty percent of all respondents reported use of a water purification system in their home. The percentage of systems installed since the date when the public were informed of the high levels of uranium in the water was highest in Group A at 27% as compared to 5% and 7% in groups B and C respectively.

Only 44 (12%) of adult participants took the opportunity to comment on their individual experiences or concerns in relation to this matter. A wide range of issues were identified either directly or indirectly related to the drinking water from the relevant supply. Some people expressed their concern regarding the possible effects of consumption of the water. Others chose to give further information about their residential history, personal medical history and sources of drinking water. There were a number of comments about the smell and hardness of the current water supply as well as the importance of ongoing testing of the quality of the water.

DISCUSSION AND CONCLUSIONS

Following the detection of higher than expected uranium levels (93-142µg/L) in 2002 in one of the three drinking water supplies to the town of Baltinglass, County Wicklow, a detailed public health study was carried out on the local population. This was the largest study to date in this field of research internationally, and the first such study in Ireland.

A multi-disciplinary group from the Department of Public Health, Health Service Executive Eastern Region, the Health Service Executive South Western Area, the Department of Public Health Medicine and Epidemiology, University College Dublin and The Adelaide and Meath Hospital, Dublin incorporating The National Children's Hospital undertook the investigation to determine whether exposure to uranium had led to health effects in the local population.

The main finding of our study was that exposure to uranium was not associated with any discernable health effects. This finding is consistent with major studies worldwide, in that sub-clinical effects on the kidney have only been tentatively suggested following exposure to much higher levels of uranium than applied in our study.

A number of studies have sought to determine whether uranium in drinking water is associated with any health effects. It is noteworthy that some of these studies involved very high levels of exposure. The maximum uranium concentration of 142µg/L in our study was quite modest in comparison with the maximum levels described in other major studies including 781µg/L in Nova Scotia, 1,920µg/L in Finland, and 7780µg/L in South Carolina.[7,8,9] In none of these studies were any clinical effects from uranium exposure found.

The international literature suggests that the kidney is the organ most sensitive to the effects of uranium, and that the part of the kidney most vulnerable is the proximal tubule.[3,4,5] This is in keeping with the chemical properties of uranium as a heavy metal. Natural uranium is slightly radioactive and international research has been unable to find any evidence that ingestion of natural uranium leads to any adverse health effects relating to this aspect. Hence, our focus was on the possible chemical effects of uranium on the kidney. A series of kidney tests were used as biomarkers to detect even minor changes in kidney function.

The population of Baltinglass was classified into three groups based on the geographical distribution of the public drinking water supplies: Group A comprised those most recently exposed to the well, Group B comprised a sample of those whose homes were supplied by this well some years previously and Group C comprised a sample of those whose domestic water supply was never from the well. The main study population consisted of 545 adults and children.

As a result of extensive local advertisement, persistent efforts to contact households and the provision of evening clinics, the final household response rate to the study was very satisfactory at 71%. The study had adequate power to detect effects similar to those reported in other studies.

Approximately 8% of participants were referred to their general practitioner for the management of health problems such as high blood pressure or suspected cystitis. It is interesting to note that the rate was similar in the three groups being slightly lower in groups A and B (7%) than in Group C (11%).

Where further follow-up was required, participants were referred to a consultant nephrologist. It is interesting to note that such follow-up of patients was not generally carried out in the studies mentioned above. The rate of referral for nephrology opinion was similar in all three groups, being marginally lower in Group A at 5% as compared to 6% and 7% in groups B and C respectively. Given the occurrence of kidney disease of approximately 11% identified in a large American study[32] we had expected to see a greater number of specialist referrals. We have identified only three persons with previously undiagnosed kidney dysfunction none of which were associated with exposure to uranium. Of critical importance is that we found no case of kidney disease due to uranium exposure.

Our study did not detect any association between uranium exposure based on where participants lived and the duration of residence in the area, the volume of water consumed or biomarkers of exposure with indicators of kidney dysfunction. This finding is consistent with the international literature, which suggests that slight changes in kidney function may occur only where uranium levels are well in excess of those measured in our study.(8)

Research conducted by Zamora et al in Canada in a similar context to this demonstrated a correlation between uranium intake and two markers of tubular dysfunction namely beta-2-microglobulin and urinary glucose.(7) We did not detect an increased prevalence of raised tubular markers in the more exposed groups using beta-2-microglobulin or retinol binding protein. In addition we did not find any association between exposure, whether based on water consumption or actual urinary uranium levels, and these tubular markers. However, as indicated above, participants in the Canadian study had been exposed to higher levels of uranium in their water.

The larger Finnish study showed an association between uranium exposure and some indicators of altered kidney tubular function, namely fractional excretion of calcium and phosphate.(8) However, it is important to note that these parameters remained within normal ranges and the association only became statistically significant at exposure levels of 300µg/L or higher. In addition the researchers did not find an association between uranium exposure and excretion of beta-2-microglobulin. The detection of only subtle changes of kidney tubular function at such high exposure levels as were described in the above studies is consistent with our inability to demonstrate any such changes given our much lower exposure levels.

We did not detect any association between uranium exposure and evidence of renal glomerular changes using urinary albumin and serum creatinine as indicators. These results are consistent with data from animal studies which suggest that the extent of kidney effects is dose dependent and that the proximal tubule is the most sensitive part of the kidney.(3,5) The results of the studies by both the Canadian and Finnish researchers were consistent with this, in that they did not find any association between exposure to uranium and indicators of glomerular injury.(7,8) It would have been surprising therefore, had we found glomerular changes in the absence of any evidence of tubular effects.

We did not find that duration of exposure was associated with any tubular or glomerular changes. This finding is in keeping with the results of the Finnish study, which did not show any association between either duration of exposure or cumulative uranium intake and effects on the proximal tubule.[(8)] These authors concluded that the kidney effects of uranium are not likely to be cumulative. Animal studies lend support to this theory. In addition repair and regeneration of the renal tubular epithelium has been observed following discontinuation of exposure.[(3,5)]

Collagen IV is under consideration as a potential marker of kidney disease. There are a limited number of studies of this novel biomarker and the clinical relevance of raised levels remains uncertain. However, it was anticipated that the use of such a potentially valuable non-invasive test in a large study of this kind, in parallel with a series of well-established tests, might serve to clarify its role. In comparison with recognised markers of tubular damage such as beta-2-microglobulin and retinol binding protein we did not find that collagen IV yielded any additional information. Furthermore, the marked variation on repeat testing of individuals and inconsistencies in repeat assays of the same specimen as well as its apparent variation with age, gender, time of day and possibly exercise have led us to question its usefulness as a screening test in the community setting.

Urinary levels of uranium were determined as an indicator of exposure. As anticipated, residents in areas most recently supplied by the well in question were found to have somewhat higher levels and these results correlated with exposure estimates using the questionnaire. Given that we measured the levels some eight to ten months after discontinuation of the water supply, we were in a position to directly compare our results with those measured in the South Carolina study at a similar time interval since exposure.[(9)] Thus the mean level of those most recently exposed (25pmol/mmol) can be contrasted with that found in the South Carolina study (127pmol/mmol). As in that study we also found a marked reduction in levels on retesting a number of months later. Given that the body gradually excretes any remaining traces of uranium over time, this latter finding was unsurprising. It is interesting to note, however, that we found that over 80% of uranium levels in the more exposed group were within normal limits, whereas Orloff et al found that almost 90% of measurements were above their reference value. It is likely that these findings can be explained by the fact that the mean water levels were over 600µg/L in the South Carolina study as compared to levels of less than 150µg/L in our study.

In line with usual clinical practice a number of spot urine samples had to be repeated using morning urine samples where possible and most of these gave normal results. The use of spot urine samples is particularly susceptible to the influence of orthostatic proteinuria (an excess of proteins in the urine related to posture and exercise) that can only be avoided by using early morning or timed samples. However, these latter tests are logistically more difficult to carry out in a community setting.[22]

The general health and well being of the three study groups was found to be broadly similar. However, as might be expected, we found a higher level of general concern in the more exposed group and this finding was reflected in the recent purchase of water purification equipment for the home. However, such equipment would only impact on the level of uranium in water if designed for this purpose.

In conclusion, our study found that the consumption of drinking water containing uranium at modestly raised levels has no discernable effect on kidney function despite using a range of sensitive and specific tests and referral for a consultant nephrology opinion where indicated. In addition no effects on general health and well being were observed. These findings are consistent with the world literature. Health screening of communities in the future is therefore unlikely to be of benefit unless exposure to uranium is exceptionally high.

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