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The UK Ministry of Defence controls a biological monitoring programme that includes testing for uranium in personnel who served in the Op TELIC conflict in Iraq. To help interpret the results, the MoD commissioned this study, to quantify the distribution of urinary uranium concentrations and isotope compositions, in personnel who had not served in Op TELIC.

The study used a cluster sampling approach, to select and visit bases where we might recruit a representative mix of ranks, genders, and occupational groups (combat, support and auxiliary). A standardised protocol and recruitment questionnaire were used. The urine samples collected were analysed for uranium and creatinine concentrations and (where possible) for uranium isotope $^{238}U/^{235}U$ ratio.

In all, samples from 732 eligible subjects were analysed. Uranium concentrations ranged up to over 400 $ng.l^{-1}$, somewhat higher than reference values quoted for the USA, but much lower than recorded in granite areas e.g. Finland. Isotope ratio measurements were available for samples with the highest concentrations; these all had a natural isotope signature, and no evidence of DU. The levels give no concern for health risks in the personnel studied.

On average, urinary uranium concentrations were lower in officers than in other ranks; they differed also across the Services, the Navy being lowest and the Army highest. Since even the highest values were from natural sources, we assume the differences represent differences in ingestion of natural uranium.

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CONTENTS

SUMMARY

Depleted uranium (DU) is a by-product of the processing of natural uranium for nuclear applications. It is a heavy metal with a higher ratio of the principal isotope ^{238}U to the next most abundant minor isotope ^{235}U than in natural uranium. It has a number of civilian uses, largely because of its density. It is also used in weapons; projectiles of DU have high density and can punch through heavy armour plating, and DU rounds are designed for use against tanks and armoured vehicles.

On impact, DU rounds can ignite to form an aerosol of uranium oxide particles, of which a proportion is fine enough to be inhaled. There have been widely publicised concerns that this may create health risks in Service personnel who may have been exposed in theatres of war where DU rounds have been used. All uranium is both radioactive and a poisonous heavy metal with toxicity to organs including the kidneys.

Small quantities of natural uranium are absorbed routinely from food and water, and from dust. Uranium ingested or inhaled will be gradually excreted, and can be detected and quantified in samples of urine. The MoD has introduced a programme of urine testing for uranium in British Service who served in the Iraq conflict (codenamed Op TELIC), and in civilian personnel attending. In order to help interpret the results, there was a need for a reference distribution to describe the expected range of urinary uranium excretion in individuals without recent exposure to DU.

This study was commissioned in order to characterise the distribution of urinary uranium concentrations in a representative sample of personnel from all three British Services, who had not served in Op TELIC. Cluster sampling was used, selecting a small number of sites likely to provide a representative cross-section of occupations and trades, stratified by Service, rank and gender. A detailed protocol was approved by the Naval Ethics Committee, and various site visits were arranged. A checklist was provided for local liaison staff, to standardise procedures at each site visit.

The study aimed to recruit and sample 1000 individuals, but local arrangements and operational difficulties led to a slower recruitment rate than desired, and sample collection was stopped when recruitment stood at 759. Each subject gave a urine sample, and completed a simple questionnaire. Analysis of the questionnaire data showed that coverage of gender, ranks and occupational group was reasonably representative of the Armed Forces as a whole.

The urine samples were analysed by quadrupole ICPMS for uranium concentration and separately for isotope composition. The creatinine concentration of the urine was quantified by colorimetry, and used to calculate an alternative expression of uranium concentration, per unit of creatinine, with the intention of adjusting for differences in urine dilution between samples.

There were 25 subjects who were omitted as ineligible because they reported service in Op TELIC, and two whose samples were too meagre for uranium determinations to be made, leaving 732 for statistical analysis. For 180 (25%), the urinary uranium concentration lay below the quantification limit of 1 $ng.l^{-1}$. The median concentration was 2.3 $ng.l^{-1}$, the 95th percentile 105 $ng.l^{-1}$, and the maximum recorded value 428 $ng.l^{-1}$.

After adjustment for creatinine, the median concentration was 1.9 $ng.g^{-1}$ of creatinine, the 95th percentile 121 $ng.g^{-1}$ and the maximum 556 $ng.g^{-1}$.

Determination of isotope ratio was possible only among 125 of the samples with the highest uranium concentration; all these isotope ratios identified the uranium detected as of natural origin, with no evidence of any contribution from DU.

These values were of the same order of magnitude, but a little higher, than published reference ranges, many of which are from US residents. However, they were at least an order of magnitude lower than found in Finland among civilian subjects taking water from wells drilled in granite. It is possible that some of the higher values observed in this study may be associated with residence in granite areas, but we have no data on residence history. Our observed values give no cause for concern regarding health risks.

Comparisons between sub-groups within the study showed some surprising differences in the distributions of urinary uranium concentrations. On average, concentrations were highest in the Army, and lowest in the Navy. In all Services, officers had lower concentrations on average than other ranks. Almost all of the concentrations over 100 $ng.l^{-1}$ were among the other ranks in the Army. There was no evidence of any difference between occupational groups within a Service. Given that all the higher uranium concentrations had a natural isotope ratio, the most likely explanation for these differences must lie in different levels of ingestion, perhaps from the supplies of domestic and/or bottled water, either on site or at home during leave periods.

Uranium concentrations adjusted for creatinine showed similar patterns, but also displayed a residual gender difference. This was likely due to higher creatinine concentrations in male than in female subjects. Although the purpose of adjustment for creatinine is to remove a source of variation from raw concentrations, in this study the unexplained variation in adjusted values was slightly greater than in the unadjusted, so it is not clear that adjustment for creatinine held any great advantage for this set of samples.

Given these differences, the shape of a reference distribution must depend on the constituent proportions of Services and ranks, and perhaps genders. We present the observed distributions for the whole study, and also for the restricted subset of male Army other ranks, which has somewhat higher percentage points. Reference distributions made up from other proportions could easily be constructed by stratified random re-sampling within our data set.

1 INTRODUCTION

1.1 BACKGROUND

Concerns have been expressed about the potential health effects of exposure to depleted uranium (DU) following active service in war zones where depleted uranium has been used. DU is used by the military as a component of armour piercing ordnance because of its high density, and because it can ignite on impact if the temperature exceeds 600 °C. There are also civil applications where DU's high density is an advantage, including as counterweights in aircraft, radiation shields in medical radiation therapy machines and containers for the transport of radioactive materials.

Depleted uranium is obtained as a by-product from the production of enriched uranium for nuclear power plants. The reactors require uranium with an enriched fraction of the highly reactive uranium isotope, ^{235}U. The uranium that remains has about 0.2% ^{235}U compared to 0.72% in natural uranium, and is known as depleted uranium (DU) (WHO, 2000).

On striking a hard object some 20% of the DU in a round can become aerosolised as uranium oxide, and a proportion of the aerosol will be fine enough to be inhaled. A recent review by The Royal Society (2001) concluded that it was unlikely that any excess of fatal cancers from possible radiation effects would be detected in a cohort of 10,000 soldiers followed over 50 years and that very few individuals were at risk of developing kidney disease. The lifetime risk of death from lung cancer in the most exposed individuals, however, might be double that of the general population and they could also be at risk of developing serious kidney disease in later life (a possible chemical effect of uranium).

Gulf War veterans known to have been exposed to DU are reported to have had urinary concentrations averaging 80 $ng.l^{-1}$, 7 years post-exposure, with the highest concentrations being about 30,000 $ng.l^{-1}$ (McDiarmid *et al*, 2000). McDiarmid *et al* (2000) reported some evidence of neurocognitive impairment in a few Gulf War veterans who had retained fragments of DU shrapnel, but further follow-up (McDiarmid *et al*, 2004) has shown no significant relationship of neurocognitive effects with uranium excretion in veterans without shrapnel. The individuals studied showed little evidence of impaired kidney function.

The Royal Society acknowledged that there was a great deal of uncertainty in their assessment of DU exposure and their recommendations included the need to validate the measurement of urinary DU concentrations as a measure of past exposure.

The UK Ministry of Defence (MoD) currently runs a programme of biomonitoring within Service personnel, which includes a survey of levels of uranium and depleted uranium in the urine of military and ex-military personnel who served in the Iraq conflict in 2003, codenamed Op TELIC, and in civilian personnel, such as Red Cross staff, present during that operation. Uranium is ubiquitous throughout the natural environment, and is found in varying but small amounts in rocks, soils, water, air, plants, animals and in all human beings. Average annual intakes of natural uranium by adults have been estimated to be about 500 µg from ingestion of food and water and about 0.6 µg from breathing air (www.who.int/mediacentre/factsheets/fs257/en). The uranium content of urine in the general population is not well understood but is thought to vary considerably depending on where people live, their diet and their drinking water. Therefore, in order to give a background context to levels of urinary uranium in military personnel who served in areas where depleted uranium weapons were deployed, there is a need for data on the range of concentrations and isotope ratios to be found in the general military population.

McDiarmid *et al* (2000), reporting on urinary uranium levels in US Gulf War veterans, quoted values from several other studies, with concentrations ranging from the unquantifiably low to maxima of 40 to 130 $ng.l^{-1}$. Our own pilot study of 25 male civilian hospital patients (Jones *et al*, 2005) produced a

maximum concentration of 38 ng.l^{-1}. We expected that concentrations in unexposed British Forces personnel would cover similar ranges. In contrast, studies of veterans exposed to DU, including individuals who had retained DU shrapnel, have returned values orders of magnitude higher (McDiarmid *et al*, 2000).

1.2 THIS STUDY

This study was set up to meet the need for data on the distribution of uranium excretion in serving military personnel who had not served in the Iraq conflict of 2003 (codenamed Op Telic), and who were therefore unlikely to have been recently exposed to the wartime deployment of depleted uranium rounds.

The MOD's Statement of Requirement was for the following:

- design of a normative value study in conjunction with the MOD;
- production of a protocol for the study;
- obtaining ethical clearance for the study;
- collection of the urine samples;
- storage and transport of the urine samples;
- statistical analysis of the data and reporting;
- publication of the work.

Three characteristics of the uranium detected in urine were considered important and were to be measured. The most direct measurement of concentration is mass of uranium per volume of urine. However, concentration of uranium per unit concentration of creatinine corrects for the degree of dilution of urine. Creatinine is a low molecular weight organic molecule released by muscle into the blood, and eventually excreted into urine. The amount of creatinine produced is dependent on the individual's muscle mass. Its concentration in urine largely reflects the degree of concentration of the urine (urine osmolality) which, in turn, depends upon the individual's state of water balance. Therefore concentration was to be measured in ng of uranium per litre of urine, and creatinine concentration in the urine sample also determined. The creatinine-adjusted concentration was then to be calculated as ng of uranium per mg of creatinine.

The ratio of the isotopes distinguishes depleted uranium from natural uranium, and therefore the ratio of the isotopes ^{238}U to ^{235}U was to be measured. The ratio of isotopes ^{238}U to ^{235}U in natural uranium is 137.88, and this is unchanged by passage through a human body; thus an elevated measured ratio for ^{238}U to ^{235}U would indicate that the uranium excreted contains less of the most radioactive isotope ^{235}U and therefore that there had been some exposure to DU. A ratio lower than the normal would suggest some exposure to enriched uranium, such as is used in nuclear weapons and power generation reactors.

2 AIM

The aim of this study was to characterise the overall distribution of values of urinary uranium and depleted uranium concentrations in military personnel in all three services, who did not serve in the conflict in Iraq in 2003 (codename Op TELIC).

3 METHODS

3.1 DESIGN CONSIDERATIONS

The principal design challenge was to construct a design by which a sample of service personnel representative of the three services could be visited, and urine samples and background data collected from them efficiently. It was clear that simply deriving a random sample of all service personnel, e.g. from payroll data, would produce a sample that was geographically scattered, and that this would not be logistically practical.

It was therefore agreed that a cluster sampling approach would be used, selecting a small number of bases that would be able to supply broadly representative service populations. Based on statistics made available through the Defence Analytical Services Agency (DASA), on staffing levels in the services, a draft sampling plan was developed. The plan was based on a limited stratification by gender and rank (officers v others). The target population was to number 1000 subjects, and specific mention was made of the need to include RN marines and Army tank crew (because colleagues in these trades, if deployed in Op TELIC, might have had battleground exposure to depleted uranium). In addition, the data and the proposed samples from the Army were further stratified into three broad occupational groups:

A Infantry/ Armour;

B Artillery/ Signals/ Engineering;

C All other trades;

This was because trades in the Army are largely organised into different units, and it would therefore facilitate the sampling to select specific units within an integrated Army base to meet the requirements.

A provisional sampling scheme that met these conditions is included as Tables 1 to 4 in the appended study Protocol (Appendix 1).

3.2 ETHICAL APPROVAL

There is no single Ethics Committee dealing with all the services. It was agreed with the MOD that the study protocol would be submitted to the Ministry of Defence (Navy) Personnel Research Ethics Committee for scrutiny; and that clearance by that Committee would suffice for all the services (Ministry of Defence (Navy), Personnel Research Ethics Committee, 2002).

Submission was made, and amendments were made to the protocol to meet the Committee's requirements. The protocol in Appendix 1 is the final document agreed and cleared by the Committee in February 2004.

3.3 SELECTION OF STUDY SUBJECTS

Discussion regarding which sites to visit, and how exactly individuals should be selected at each site to achieve the sampling plan, ran through several cycles. At a meeting in August 2003, senior DASA staff had advised that random sampling from personnel lists at individual bases was likely to be impractical. It was therefore agreed that, once high-level authorisation was granted, IOM staff should work directly with nominated officials at carefully selected sites to recruit volunteers representative of the available range of ranks and occupations, in such a way as to honour the intended representativeness of the sampling scheme proposed in the protocol. It was anticipated that there would be perhaps ten locations.

This strategy was adopted, in the knowledge that analysis of the data collected would allow distinctions to be made between the intended strata, even if the achieved proportions were not exactly as in the proposed sampling scheme.

3.4 FIELD SURVEY METHODS

3.4.1 Preparation and liaison

The MOD identified suitable field survey sites at UK Service bases that would meet the requirements of the sample profile. The names of nominated officials for each site were then provided to IOM. Initial telephone and/or email contact with the site was then initiated by the IOM project team leader. The study protocol was sent to the nominated official and further discussions took place to ensure the requirements for each site's contribution to the overall study were fully understood. The nominated official had overall responsibility for the on-site organisation and administration but normal practice was to delegate a liaison officer to work with the IOM and assist with the practicalities of the field survey organisation. This person was designated by IOM as the Local Liaison Officer (LLO). The LLO was contacted by IOM staff to discuss the particular requirements for the field survey and the practicalities of organising volunteer recruits to attend at survey. Details of the sample profile required, in terms of numbers of officer/other rank; male/female; were sent to both the nominated site official and to the LLO. A representative selection from all occupational groups was requested but was not specified numerically.

A document outlining the requirements and issues involved in organising and running the field survey was written and a copy of this was sent to the LLO. This "Liaison Information Sheet" is included here as Appendix 2. It spells out the detailed requirements for the field survey and outlines the responsibilities of all staff involved. It also identifies the IOM project team and their responsibilities during this phase of the project.

The IOM project leader and/or the field survey coordinator offered to visit the site and meet with the LLO and other staff involved in the survey administration. The purpose of this meeting was to go through the field survey procedures and requirements with the site based staff and give advice on how to best prepare for the field survey. An on-site meeting also allowed IOM staff to check that any proposed facilities were suitable for the field survey to operate efficiently. This on-site meeting was requested and organised by the IOM for the first field survey that was arranged (RAF Leuchars) and was subsequently suggested to all other sites to be surveyed. The second RAF site (RAF Marham) was the only other site to accept the offer of this meeting while other sites declined. The majority of LLO's considered that they had adequate information from the supplied documentation and from discussions with IOM staff and that an on-site meeting was not required.

IOM supplied Subject Information Sheets (Annex A of the study protocol) which provided information about the purpose of the study. These were sent down to the LLO for distribution to potential survey recruits to provide them with the information required to make an informed decision about participation in the field survey.

3.4.2 Survey equipment

The IOM survey staff arrived on site with most of the materials and equipment required for the field surveys. This included:

- tamper evident plastic bags for urine sample bottles;
- ice packs for cooling stored samples;
- cool boxes for temporary sample storage;
- sample identity number labels;

- paper work – DU Study questionnaires, Subject Information sheets, Subject Consent forms, urine sample instruction sheet.

3.4.3 Institute of Naval Medicine (INM) materials

Plastic urine sample bottles (120ml) were provided by INM and were normally sent directly to each site. Bottles were supplied in hard travel cases, prepared and ready for the urine sample and individually enclosed in a tamper evident plastic bag. Cases were kept locked with padlocks at all stages of transportation and duplicate sets of keys were held by IOM and INM. Cases were also kept locked on site when not being attended by IOM staff.

INM supplied IOM with laser labels pre-printed with an agreed range of sample id numbers. These labels were supplied in identical pairs and were printed onto label print stock designed to withstand exposure to moisture and storage in freezers after attachment to the urine sample bottles.

3.4.4 On-site procedures

At each survey site the LLO organised for groups of volunteer subjects to attend at suitable time intervals. The LLO also provided some clerical/administrative assistance to the IOM survey staff.

On arrival, each participant was given a Subject Consent form (Annex B of the appended study protocol) to read and sign. If they had not previously seen one, each subject was also given a copy of the subject information sheet (Annex A of study protocol). Upon the return of the signed consent form, subjects were asked to complete the study questionnaire (Annex C of the study protocol).

The study questionnaire requested information on each participant's:

- name;
- date of Birth;
- gender;
- service (Army/Navy-RM/RAF);
- officer or other rank;
- service number;
- age when joined service;
- broad occupational group (see section 3.1);
- current trade;
- previous campaign record in Balkans/Gulf 1/OpTELIC;
- medically fit?

These data were mostly recorded on the questionnaire as tick boxes.

When the questionnaire was completed it was checked for completion by IOM field survey staff and then one of a pair of identical labels, printed with a unique study identity number was stuck onto the completed questionnaire and the second label was stuck onto a new urine sample bottle after removal from its tamper evident wrapper. Instruction sheets were available to each subject explaining the procedure for supplying the urine sample. These were as below:

- Wash and dry your hands prior to providing a urine sample
- Do not remove cap of bottle until you are about to provide a urine sample.
- Provide your specimen in the privacy of a toilet stall/cubicle
- You should provide about 100 mls of urine (fill to just below the shoulder of the bottle)
- Replace bottle cap as soon as sample is completed
- If necessary wipe the outside of the bottle with paper towel or toilet tissue
- Return specimen bottle to the collection staff

- Your specimen will be placed in a tamper proof bag in your presence

Subjects returned completed urine sample bottles to IOM staff who then supervised the process of putting sample bottles into tamper proof plastic bags and sealing them. Samples were then stored in cool boxes. If the samples were not being transported to INM on the day of survey, the samples were kept refrigerated until the next day.

3.4.5 Sample transfer

Samples were transferred to the transport cases supplied by INM. Samples were kept cool with icepacks and prepared for transport to INM laboratories. A majority of the sample cases were collected directly by INM staff on the day of survey and transported back to INM laboratories. Samples from the Scottish service bases were transported by overnight courier in locked containers supplied by INM. Samples were kept cooled by icepacks. The cases were designed to hold samples and icepacks firmly with minimal movement during transportation. All samples were received back by INM in good condition.

Upon receipt at INM all samples were registered and allocated a laboratory number. An aliquot was then taken for creatinine analysis. This was split into two portions. The first was analysed straight away and the second frozen for later reanalysis to check for stability over time. Once registered the samples were stored in dedicated refrigerators in a room retained purely for the handling of the urine samples from this study. The creatinine values reported were those from the frozen samples.

3.5 SAMPLE ANALYSIS

3.5.1 Analysis of total uranium in urine

Total uranium in urine was determined by INM method I075, which was developed in-house based on the published method of Lorber et al (1996) and is UKAS accredited.

The method uses a Perkin Elmer Elan 6100 quadrupole ICPMS with a FIAS 400 flow injection sample introduction system which is tuned for optimum sensitivity at mass 238. Urine samples are introduced directly via the FIAS with no prior treatment and the total uranium content is measured as ^{238}U against matrix matched calibration standards set up using urine from non-exposed individuals.

All materials, reagents and pooled urine are rigorously batch tested prior to use.

The method is calibrated across the range 0-40ng.l^{-1} using traceable uranium standards spiked into pooled urine, endogenous uranium in the calibration standards is blank corrected. Samples showing higher concentrations are diluted to fall within the calibration range. Within each analysis three levels of QC are run to bracket each batch of 10 samples. These are pooled urine spiked at 2.5, 15 and 30ng.l^{-1} with a traceable uranium standard independent of the calibration standard. All QC data is assessed using Shewhart control charts.

The method provides linear calibrations better than 0.999 and spike recoveries better than 98%. Between run CV at 15ng.l^{-1} is 8.1% and the estimated limit of quantification is 1ng.l^{-1}.

3.5.2 Analysis of uranium isotope composition

Analysis of the urine samples for uranium isotope ratio was carried out using INM method I077, which was developed in-house for biological monitoring of in-theatre uranium exposure. The method has been validated for accreditation but is not yet accredited. The method was intended as a screening method and as such will only produce reliable isotope ratio data for samples with 8ng.l^{-1} total uranium or greater.

Urine samples are analysed by inductively coupled plasma mass spectrometry (ICP-MS) using a Perkin Elmer Elan DRCII quadrupole ICPMS in isotope ratio mode. Certified uranium Isotope Reference Materials (IRMs) are used for the correction of mass bias of the mass spectrometer and Quality Control purposes. Certified isotopic reference materials IRMM-183 and IRMM-184, obtained from the Institute for Reference Materials and Measurements (IRMM), are used to prepare solutions for mass bias correction and quality control procedures.

Prior to each use the Elan DRCII is optimised for uranium intensity and confirmed by system suitability checks.

Standards, QC and samples are analysed directly in Isotope Ratio mode. The uranium 235 and 238 counts are measured in very rapid succession with the dwell time of the instrument adjusted to allow much more time counting the 235 signal to compensate for the difference in the ratio abundance of the two isotopes. Six replicate readings are taken for each sample and the mean isotope ratio is the figure reported.

Non-spectroscopic interferences, such as suppression of ionisation in the ICP plasma due to high salt concentrations, are minimised by the use of both matrix matched calibration standards. Mass bias is corrected using a 20ng.l^{-1} natural uranium certified isotope ratio solution, the certificated ratio value being entered into the instrument software to calculate a correction factor.

Sample and QC isotope ratios are calculated relative to the standard isotope ratio obtained. Blank correction is achieved with the use of the pooled urine used to prepare the standard and QC solutions.

Isotope ratio values obtained for the QC spikes are used to assess the sample results acceptability. Shewhart Control charts and comparison to the expected data are used to assess the QC results.

3.5.3 Determination of creatinine in urine

The method used for determination of creatinine in urine was based on the Jaffe reaction, which is a kinetic colour test. Creatinine forms a yellow-orange colour with picric acid in an alkaline medium. The level of creatinine in a sample is proportional to the rate of change in absorbance at 520/800 nm, which was measured with an Cobas Mira-S clinical analyser. The analysis was accredited to UKAS/ISO 17025.

3.5.4 A note on units for creatinine

Creatinine concentrations in urine may be reported in mass units per volume or in moles per volume. The molecular weight of creatinine is 113, and one mole is equivalent to 113 g; 1 g of creatinine equals 8.8 mmol. These factors are used to convert between creatinine concentrations reported in different units, and between concentrations of uranium adjusted for creatinine.

3.6 DATA PROCESSING

The data obtained for the study included the information from the recruitment questionnaire and the measurements on the samples, i.e. for each sample: volume, total uranium concentration (as mass per unit volume of urine), creatinine concentration and uranium concentration normalised to creatinine concentration, plus (where measurable) the ratio of the concentrations of the isotopes ^{238}U to ^{235}U.

Questionnaire data were entered to computer file. Appropriate procedures were designed and implemented to check the collected data for logical consistency, valid values, valid ranges and cross-record consistency. A few missing data items such as service numbers or dates of birth were checked by contacting the LLO at the survey sites who was normally able to supply the missing data from station administrative records.

The analytical laboratory provided the urine test results electronically in an Excel spreadsheet. These were matched to the questionnaire data in an MS Access database.

All of the study data files were stored on a *Compaq* Server on the IOM's network, located in a secure, climate controlled computer room into which physical access is controlled and limited to IT staff. Access to study data was restricted to IOM project staff. The IOM's IT Security Policies include issues of data security and the integrity of all computerised data. These procedures included a daily, full-backup procedure, active protection from computer viruses and prevention of unauthorised access to any study data. The study ran in full compliance with the Data Protection Act. (The IOM was the data controller under the Data Protection Act.)

A file for analysis was exported in an MS Excel file that identified participants only by the IOM's study participant identity number, to maintain confidentiality throughout the statistical analyses. No individual participant is identified in this report.

3.7 STATISTICAL ANALYSIS

Following data validation, the data were organised for presentation in tables and graphs.

Formal statistical analyses of the unadjusted and adjusted uranium concentrations, and of the $^{238}U/^{235}U$ isotope ratio, had the following aims:

1. to establish to what extent the achieved sample of individual subjects met the intended criteria of representativeness;

2. to quantify the distribution of variation between individuals;

3. to test for systematic differences in the distributions by gender, rank and occupation.

Analyses for aim 3 were performed as Analyses of Variance (ANOVA) using linear regression techniques, with graphical checks on the distribution of residuals. These checks confirmed that an appropriate scale for analysis of all the variables was the logarithms of the measured concentrations.

All the analyses were carried out using the statistical package GenStat (GenStat Committee, 2002).

4 RESULTS

4.1 RECRUITMENT

4.1.1 The sample achieved

RAF Leuchars, being geographically closest to IOM's HQ, was selected for the first site visit, to prove the procedures. The local arrangements were made with staff of the Medical Centre, who were helpful, incisive and efficient. The sampling visit passed off very successfully. Feedback from the Leuchars staff was invaluable in setting up the sampling visit for RAF Marham, which again was successful.

For the Army, partly due to the multiplicity of units involved, it was harder to arrange who at each base should liaise with IOM. After a number of discussions with various contacts, we received advice to concentrate on 12 Mech Bde as the source of the Army sample, which included KRH, a tank unit. Subsequent advice was that sampling within 12 Mech Bde would be best organised around the Bulford/ Tidworth area.

The first visit was only partially successful, despite the efforts of local liaison staff to ensure that arrangements for the visit would be in place. A later visit was somewhat more successful, although it still left us short of the final target for Army personnel.

For the Navy, it proved difficult to establish contact with staff at Faslane. A pre-visit was declined but eventually visits were planned. In the end, after one planned visit was cancelled, we made two separate visits, but were disappointed to achieve only part of the target sample.

It was agreed to obtain the remaining requirement of the sampling for naval personnel at Portsmouth. However, two visits here were only partially successful, and still left us well short of the target sample. The deficit in marines was to be made up by sampling at Poole, but there were further organisational problems and, again, sampling fell short of the target.

We waited some months for contact from a third RAF base. Finally we were contacted by the Medical Centre at RAF Lyneham, and were making arrangements to sample there when we were instructed, as a result of all the delays, to cease sampling entirely. Lyneham had recently suffered a fatal troop transport accident, which had obviously upset and distracted staff there considerably, but we believe that the sampling there would probably have been as successful as it was at the other RAF bases.

Table 4.1 details the sampling visits made by IOM staff, and compares the target sampling numbers at each site with what was finally achieved. (The targets were set sequentially, in the light of any underachievement at previous visits, and do not sum to the total sample numbers required.) When the sampling was terminated, we had achieved around 75% of the planned sample.

Table 4.2 shows the distribution of the achieved sample by Force, rank, unit and gender, omitting 25 subjects who replied "Yes" to the recruitment questionnaire's question on deployment to Op TELIC, and who were therefore ineligible, and two low volume samples for which determinations of uranium concentration could not be made. The numbers are broken down into three main occupational groups; these correspond to the distinctions labelled A, B and C for the Army samples in the Protocol, generalised as appropriate to the other Services. The planned sample sizes according to the draft in the Protocol are labelled "*Plan*" and shown in italics, and the actual numbers achieved are labelled "Ach". Note that the final version of the Protocol did not specify the breakdown of the samples for the Navy and Air Force into occupational groups, but did for the Army.

We see that both the Navy and the Air Force supplied about two-thirds of the planned sample, while the visits to Army bases had provided almost 80% of the planned sample. In addition, the Army sample had, as planned, a predominance of combat troops, even if the relative distribution to occupational groups was not exactly as planned (particularly between support and auxiliary occupations).

Table 4.1 Site visits and number of subjects recruited against target

Start Date	Site	Target	Achieved
05/05/04	RAF Leuchars	100	100
08/07/04} 15/07/04}	RN Faslane	75	46
25/07/04	RAF Marham	100	100
26/07/04	RN Portsmouth (HMS Invincible)	150	28
29/07/04	Tidworth	500	151
22/11/04	RN Portsmouth (Various)	120	52
09/12/04	RM Poole	50	18
17/02/05	Bulford Barracks/ Aldershot	350	264
TOTAL			**759**

Table 4.2 Eligible subjects recruited, by Service, occupational group, rank and gender, compared with that planned in the protocol.

Service	Occupational Group	Female				Male				Total	
		Officer		Other Ranks		Officer		Other Ranks			
		Plan	Ach	*Plan*	Ach	*Plan*	Ach	*Plan*	Ach	*Plan*	Ach
Army	Combat	*0*	0	*0*	0	*35*	31	*363*	275	*398*	310
	Support	*0*	1	*0*	1	*2*	2	*20*	39	*22*	43
	Auxiliary	*2*	2	*13*	9	*6*	5	*59*	33	*80*	49
	Total	***2***	**3**	***13***	**10**	***43***	**38**	***442***	**347**	***500***	**398**
Navy	Combat		1		3		9		49		62
	Support		0		3		4		38		45
	Auxiliary		0		5		4		21		30
	Total	***5***	**1**	***25***	**11**	***28***	**17**	***142***	**108**	***200***	**137**
RAF	Combat		1		0		5		3		9
	Support		0		7		11		78		96
	Auxiliary		6		14		17		55		92
	Total	***6***	**7**	***24***	**21**	***54***	**33**	***216***	**136**	***300***	**197**
All Services		***13***	**11**	***62***	**42**	***125***	**88**	***800***	**591**	***1000***	**732**

4.1.2 Representativeness of sample

It is appropriate and necessary to consider to what extent this sample, limited by the practical constraints of geography, logistics and co-operation, can be considered representative of the armed forces as a whole. Information about deployed strength was taken into account in constructing the sample sizes.

Although the initial plan had been for sample selection by stratified random sampling, the approach finally agreed was to select appropriate sites and ask local liaison officers to arrange sampling, to agreed numbers by gender and rank, to give a mix of occupations that they considered representative. These judgments were made locally at carefully selected sites.

To assess the representativeness of the achieved sample, we obtained from DASA figures on the deployed strengths of the forces as at April 2004 and 2005, broken down by Service, occupational group, gender and rank. These were very similar: since the sampling took place between these dates, we calculate an average strength as the simple average of the 2004 and 2005 data. The averages are shown in Table 4.3.

Table 4.3 Average strength by Service, occupational group, rank and gender, 2004-2005.

Service	Occupational Group	Female		Male	
		Officer	Other Ranks	Officer	Other Ranks
Army	Combat	20	50	4205	28700
	Support	300	1285	3145	21790
	Auxiliary	980	4750	4080	28250
Navy	Combat	160	835	2755	6720
	Support	100	245	1895	9020
	Auxiliary	245	1600	1530	10785
RAF	Combat	420	525	4430	4325
	Support	85	450	1665	15340
	Auxiliary	680	3440	2345	15080

Table 4.4 presents the actual samples achieved, from Table 4.2, as a fraction (numbers per thousand) of those in Table 4.3. Values calculated with denominators of fewer than 100 are shown in brackets.

Amongst males, who were the large majority of the actual and target populations, the samples from the Army and Navy had a preponderance of combat forces, as was intended. In the RAF, the proportion of combatants was quite low in officers, and lower still among other ranks. Overall, there was some representation of all three occupational groups in all the Services at officer and other ranks.

The much smaller numbers of female staff sampled led to quite variable proportions, particularly in officers. However, in all the Services there was some coverage of the non-combat occupations, as desired.

Overall, considering Table 4.2 and 4.4, we consider that the sampling has achieved a broadly representative sample, with perhaps some under-representation of the (relatively small) group of RAF combat personnel, particularly from the other ranks. While down in absolute numbers, the Navy response was reasonably distributed across groups. In the Army, the greater representation of male combat personnel was broadly as planned.

Table 4.4 Proportional representation by sample of Forces strength 2004-2005: numbers sampled per thousand.

Service	Occupational Group	Female		Male	
		Officer	Other Ranks	Officer	Other Ranks
Army	Combat	(0.0)	(0.0)	7.4	9.6
	Support	3.3	0.8	0.6	1.8
	Auxiliary	2.0	2.0	1.2	1.2
Navy	Combat	6.2	3.6	3.3	7.3
	Support	0.0	12.2	2.1	4.2
	Auxiliary	0.0	3.1	2.6	1.9
RAF	Combat	2.4	0.0	1.1	0.7
	Support	(0.0)	15.6	6.6	5.1
	Auxiliary	8.8	4.1	7.2	3.6

4.2 DISTRIBUTIONS OF URANIUM CONCENTRATIONS

4.2.1 Distribution of uranium concentrations in urine

INM conducted analyses for all 759 urine samples sent. In two cases, there was insufficient sample volume to analyse for uranium, and the results for uranium concentrations are therefore missing. In another 185 cases, the amount of uranium present was so small as to preclude quantification: in those cases, the concentration was reported as <1.0 $ng.l^{-1}$. In the remaining 572 cases, a quantitative concentration estimate was supplied.

Of the 757 subjects with a uranium concentration determination, 25 had recorded on their recruitment questionnaire that they had served in Op TELIC, and were therefore not eligible subjects. With their omission, there were 732 subjects with determinations of uranium in urine, of which 180 were recorded as below 1.0 $ng.l^{-1}$.

Figure 4.1 shows the cumulative frequency distribution of these values. This graph is a percentile-percentile probability plot. The x-axis shows the uranium concentrations in $ng.l^{-1}$, while the y-axis

shows the expected standard normal deviate corresponding to the rank of the observation. The values recorded as <1.0 ng.l^{-1} have been graphed at a concentration of 0.6; it is customary in such cases to substitute a value around one-half or two-thirds of the smallest quantified value, so we have used 0.6. Since there were 180 values <1.0 ng.l^{-1} within the eligible subjects, they share the tied average rank of (180+1)/2 = 90.5; however, this has no effect on the shape of the graph at concentrations above 1 ng.l^{-1}.

The graph may be used to read off percentile values in either direction, for concentrations from 1 ng.l^{-1} upwards. Thus we can see from the graph that about 25% of concentrations lay below 1 ng.l^{-1}. (As we have noted, the exact number recorded as < 1 ng.l^{-1} was 180 from 732). The 95th percentile is a little over 100 ng.l^{-1}, so only 5% of the values are higher than this.

Since the concentrations are on a logarithmic scale and the probabilities on the axis are scaled to the Normal distribution, the graph would be a straight line if the data were a sample from a lognormal distribution, as is often found for contaminant concentrations in human subjects. It is not, but then we have no reason to expect it to be. In particular, if uranium concentration were affected by external factors, then the overall distribution would be affected by the strength of those effects, and the

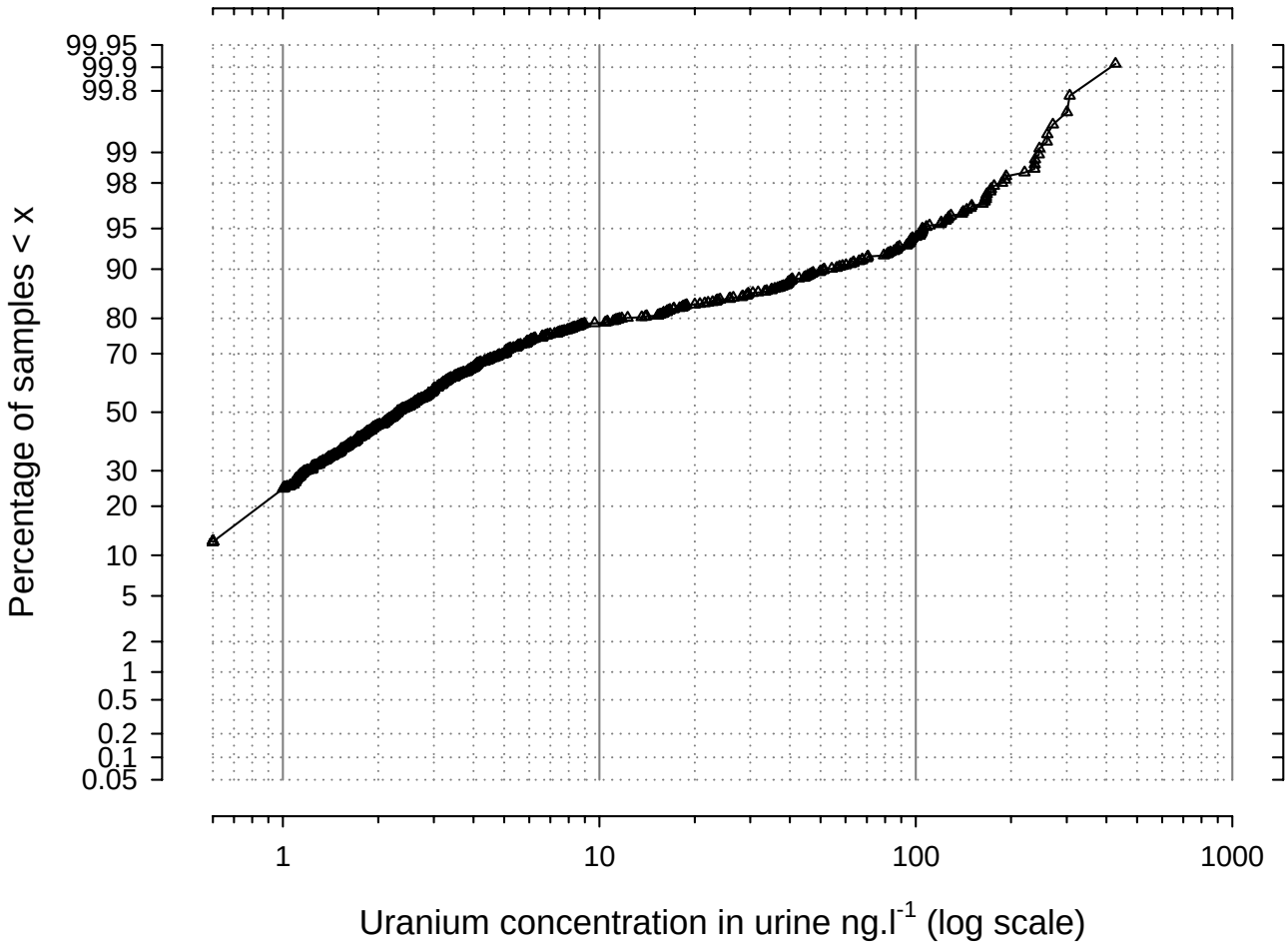

Figure 4.1 Lognormal probability plot of urinary uranium concentrations: all samples

distribution of the factors among the subjects studied. In Figure 4.1, the systematic departure from linearity suggests that the data are not a simple sample from a lognormal distribution, which in turn suggests that there may be inhomogeneity and possible systematic differences among the subjects. These are explored in section 4.4.

The highest concentration recorded was 427.6 ng.l^{-1}. The arithmetic mean was 18.4 (although this would change slightly if some value other than 0.6 were chosen to stand for <1.0). The median value was 2.3, and the upper percentiles were 6.6 at 75%, 51.4 at 90%, 105.0 at 95% and 244.7 at 99%.

4.2.2 Distribution of creatinine concentrations in urine

Urinary creatinine concentrations were returned for all the 759 subjects. The two samples of insufficient volume for uranium concentration determination had creatinine concentrations of 3.66 and 2.55 g.l^{-1}. Since the purpose of the creatinine concentrations was to standardise the uranium concentrations, these two samples are not considered further. Again, the 25 subjects who reported taking part in Op TELIC have been omitted, leaving 732 eligible values.

Figure 4.2 shows the cumulative frequency distribution of the creatinine concentrations of the eligible subjects, as a probability plot.

The highest creatinine concentration recorded was 4.66 g.l^{-1} and the lowest 0.11. The arithmetic mean was 1.32. The median value was 1.21, and the upper percentiles were 1.78 at 75%, 2.36 at 90%, 2.65 at 95% and 3.41 at 99%.

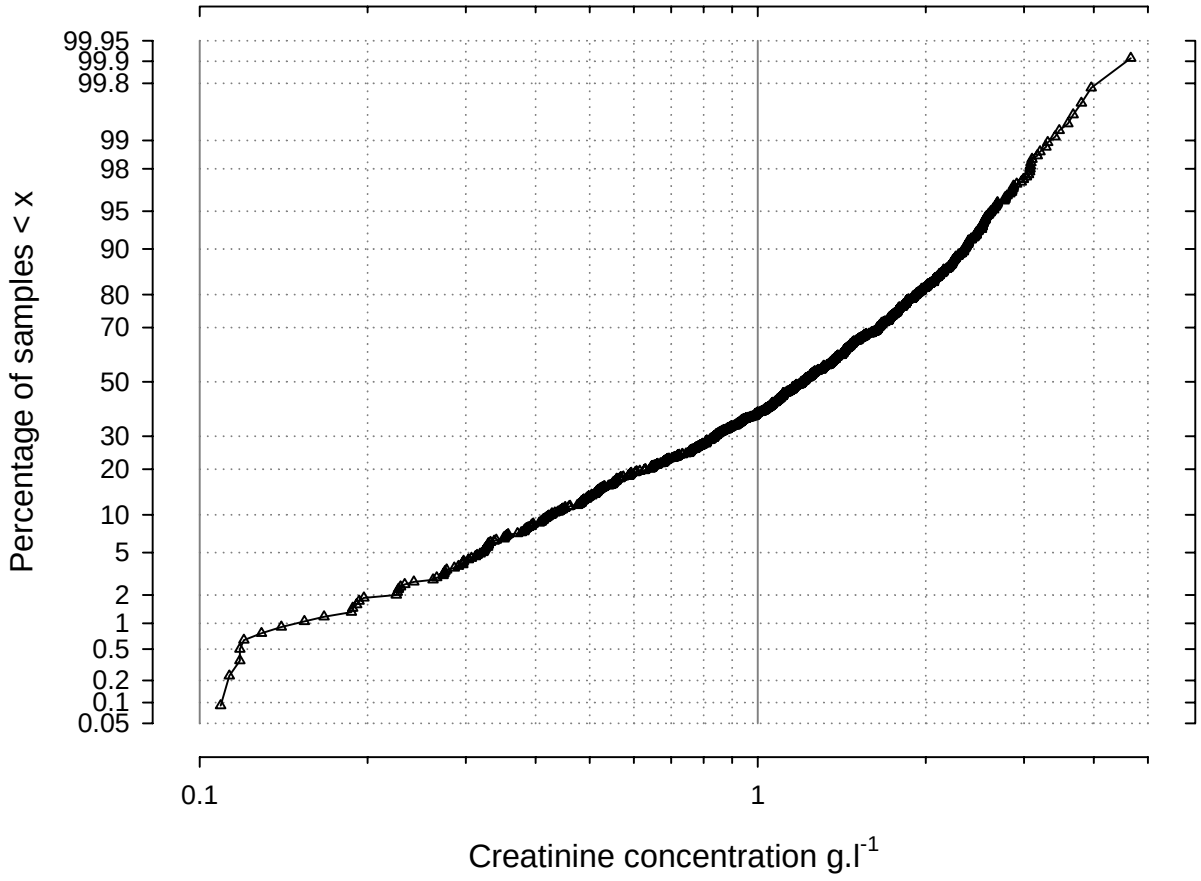

Figure 4.2 Lognormal probability plot of urinary creatinine concentrations: all samples

4.2.3 Distribution of uranium concentrations adjusted for creatinine

Adjusted uranium concentrations were calculated by dividing each by the corresponding creatinine concentration, to yield results in units of ng per g creatinine, i.e. $ng.g^{-1}$. For those samples where the uranium concentration was reported as <1.0, a notional concentration of 0.6 $ng.l^{-1}$ was adjusted by the corresponding creatinine concentration.

Figure 4.3 shows the cumulative frequency distribution of the adjusted values, as a probability plot.

The highest adjusted concentration recorded was 556.3 $ng.g^{-1}$ and the lowest 0.23 (noting that values calculated from the notional lowest uranium concentration of 0.6 predominate among the lowest adjusted concentrations). The arithmetic mean was 20.2. The median value was 1.87, and the upper percentiles were 5.6 at 75%, 47.1 at 90%, 120.9 at 95% and 288.5 at 99%.

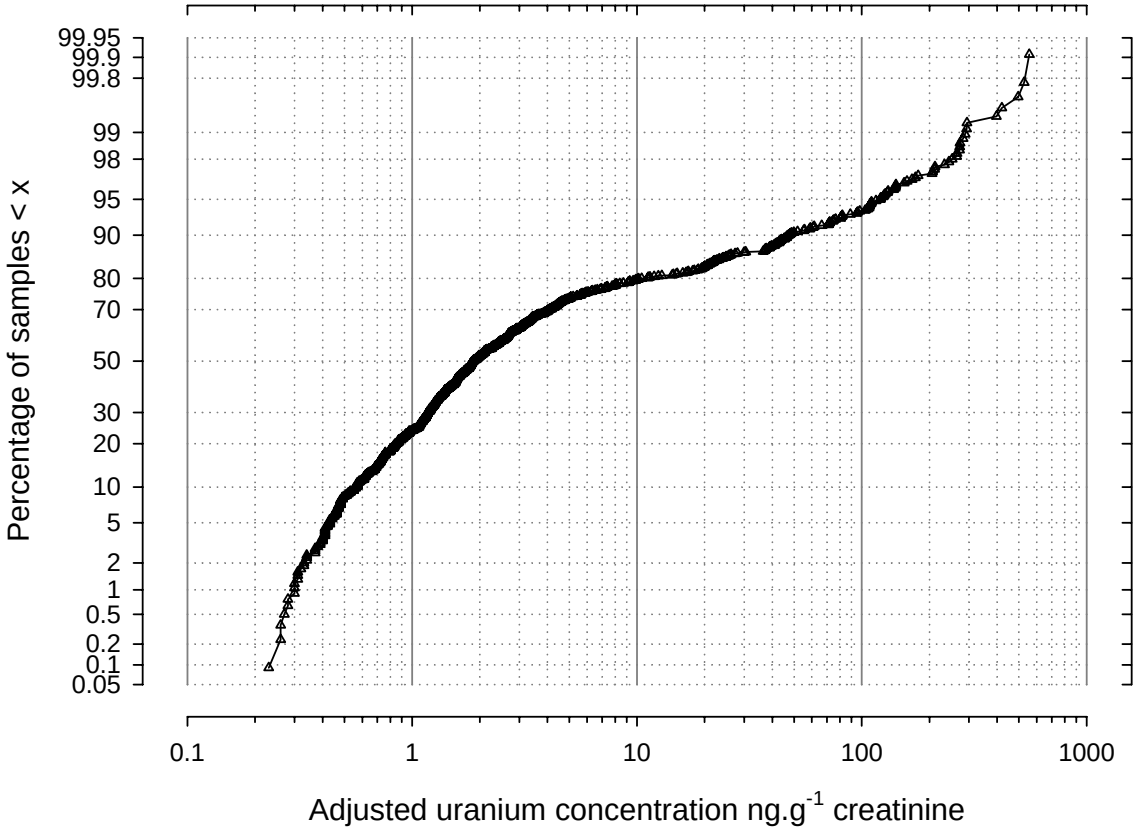

Figure 4.3 Lognormal probability plot of creatinine-adjusted uranium concentration: all samples

4.3 DISTRIBUTION OF URANIUM ISOTOPES

4.3.1 $^{238}U/ ^{235}U$ ratios

The analytical laboratory INM had declared that, where the urinary uranium concentration was below 8 $ng.l^{-1}$, it would not be possible to calculate a reliable estimate of the $^{238}U/ ^{235}U$ isotope ratio. In the event, there were technical difficulties also with some samples where the uranium concentration was

greater than 8 ng.l^{-1}, manifest as poor precision in the measured ratios. This was probably due to matrix effects, i.e. interference from other metallic ions present in the sample. The laboratory was able to return reliable isotope ^{238}U/ ^{235}U ratios for a total 125 of the samples.

The distribution of the isotope ratios is shown in Figure 4.4, where the ratios are plotted against the corresponding uranium concentrations. This graph shows no evidence of any relationship of the isotope ratio with the corresponding concentration.

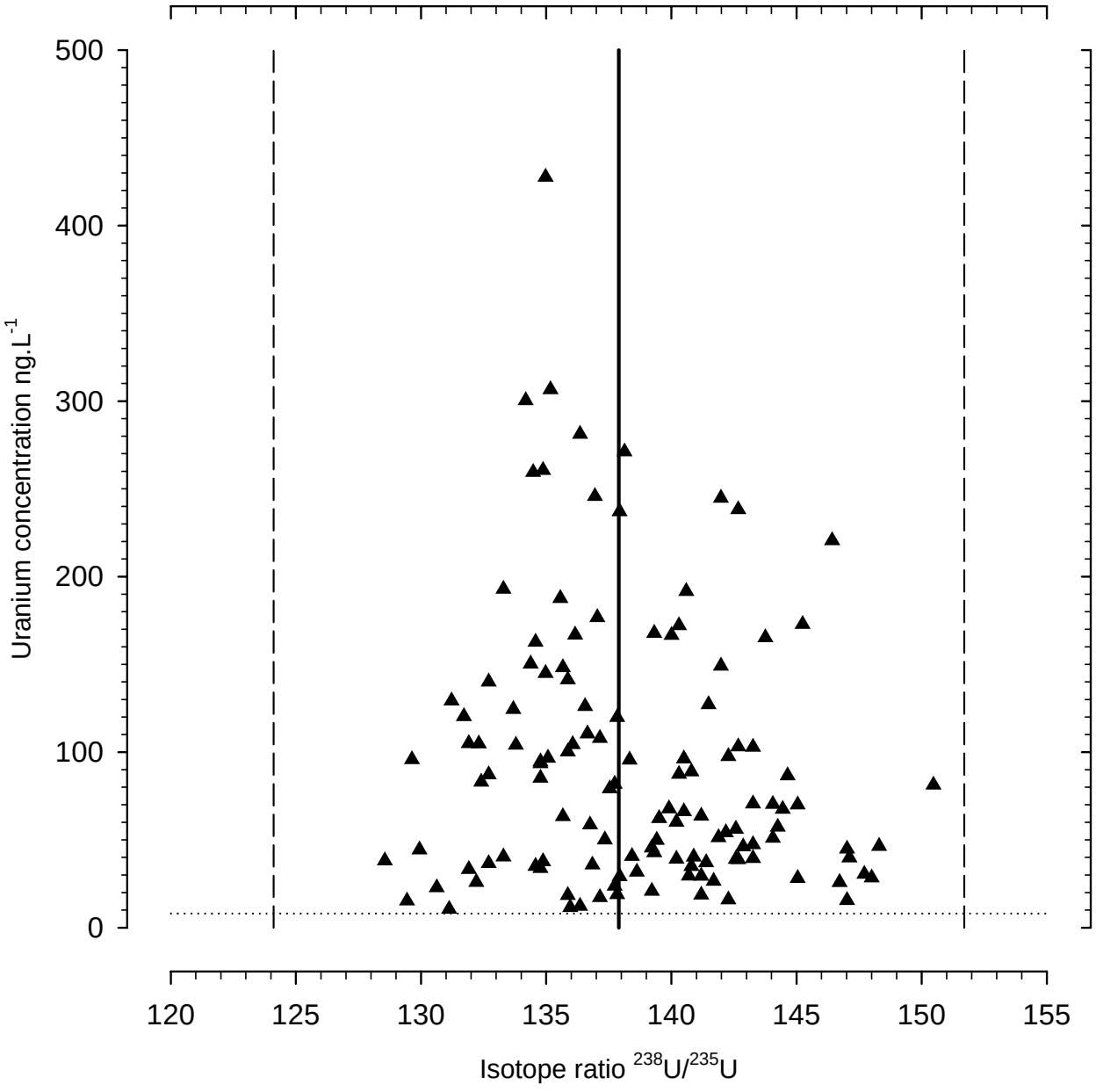

Figure 4.4 Isotope ratio ^{238}U/^{235}U vs. urinary uranium concentration

The ^{238}U/ ^{235}U ratio is measured with some error, but if large enough would be taken as evidence that the uranium excreted included some depleted uranium. The analytical laboratory's rule of thumb is that a sample should be reported as possibly showing depleted uranium if it exceeds the natural ratio

by 10%. By this convention, ratios lower than the natural standard by more than 10% could be taken as indicative of contamination with enriched uranium. The natural ratio is 137.9, which is shown in Figure 4.4 as a solid line. The dashed lines corresponding to these rule-of-thumb limits are drawn 10% above and below this, i.e. at 151.7 and 124.1.

We may see that all the ratios judged as reliable by the laboratory lie within these limits of normality. There is therefore no evidence that any of the samples shows any contamination with either depleted or enriched uranium. This implies that the uranium detected in these samples was predominantly or entirely from natural sources.

4.4 SOURCES OF VARIATION

4.4.1 Structure of analysis

Analyses of variance were performed to examine any evidence for systematic differences in average uranium concentrations between factors stratifying the sample, notably Service, rank, occupational group and gender, and their interactions. Residual plots and the stated uncertainties suggested that the requirement for equal variances was more likely to be met with analyses on the logarithmic scale than on the measured scale, and the results shown here are from analyses of the logs of the measurements. Since logarithms of zero are undefined, we followed common practice by substituting values of uranium concentration recorded as below the quantification limit of 1.0 by the notional value 0.6.

Since the distribution of the sample with respect to the stratifying factors was not balanced, the analyses were carried out using linear regression models.

4.4.2 Analysis of urinary uranium concentrations

Table 4.5 is an ANOVA table summarising the results of sequentially fitting the factors to the logarithms of urinary uranium concentrations.

Table 4.5 Summary of Analysis of Variance (ANOVA): uranium concentration in urine (log scale).

Source of variation	d.f.	Mean Square	F-ratio
Service (Army, Navy, RAF)	2	150.75	66.43
Occupational Group (OG) (Combat, Support, Auxiliary)	2	1.84	0.81
Service.OG interactions	4	0.52	0.23
Rank (Officers, Other Ranks)	1	48.82	21.51
Service.Rank	2	3.83	1.69
Rank.OG	2	0.95	0.42
Service.Rank.OG	4	0.69	0.31
Gender	1	0.30	0.13
Service.gender	2	2.19	0.97
Residual	711	2.27	
Total	731	2.72	

When testing a term against the residual variation for formal statistical significance at the 5% level, we would require an F-ratio of 3.84 for a term with 1 degree of freedom (d.f.), 3.00 for 2 d.f., and 2.37 for 4 d.f. In Table 4.5, the only terms that are significant are those for Service and Rank, which are both significant at better than the 0.1% level. The F-ratio for the interaction between the Service and Rank terms falls well short of significance. We conclude that uranium concentrations in this sample varied systematically between Services and by rank.

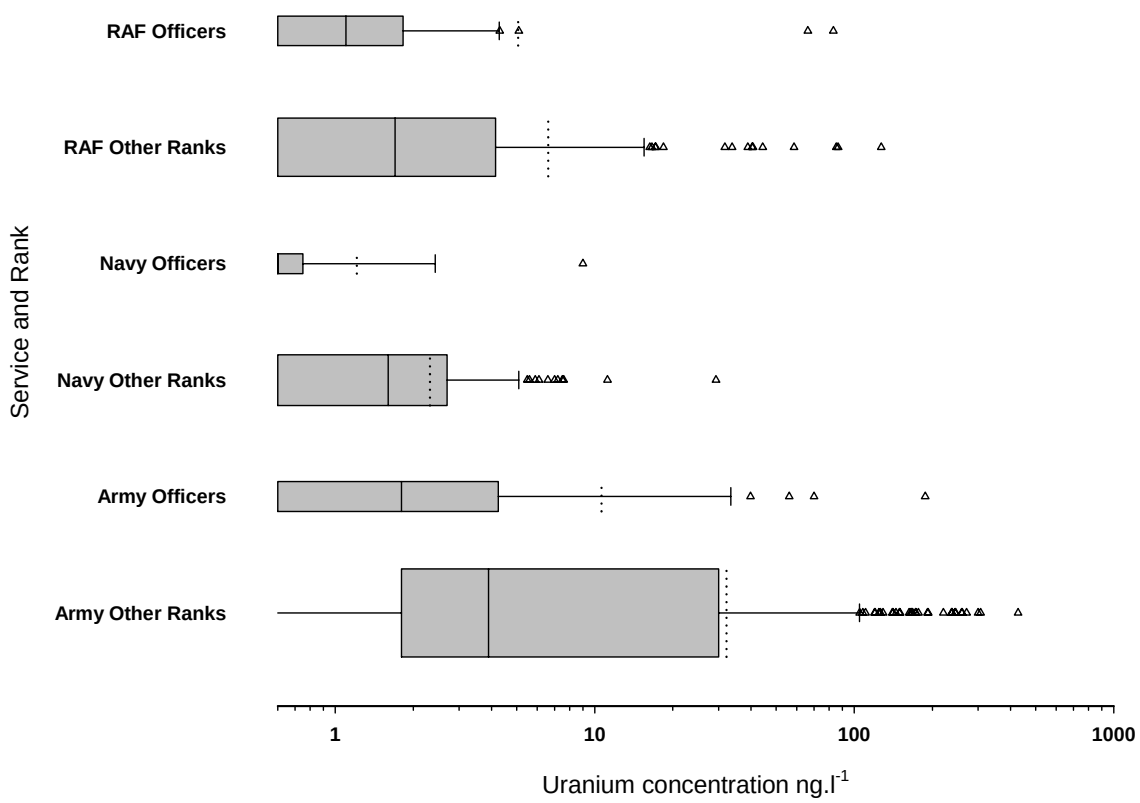

Figure 4.5 Boxplots of distributions of urinary uranium concentration by Service and rank

Figure 4.5 is a box-plot summarising the distributions of urinary uranium concentration for each combination of Service and rank. The boxplots show, for each distribution, a box drawn between the 25% and 75% point, with the median indicated as a solid line within the box, and the arithmetic mean as a dashed line. The width of the boxes is scaled to the square root of the number of observations plotted. The whiskers outside the box extend to the 10% and 90% percentiles, and values outside those limits are plotted as individual points. However, because 25% of the values were below the limit of quantification (and have the notional value 0.6), fine distinctions are not possible at the lower end of the distributions.

Figure 4.5 shows clearly the differences between the Services, and the differences between officers and other ranks within each Service.

4.4.3 Analysis of uranium concentrations adjusted for creatinine

Table 4.6 is an ANOVA table summarising the results of sequentially fitting the factors to the logarithms of creatinine-adjusted uranium concentrations.

As with the unadjusted uranium concentrations, the adjusted values show strong influences of Service and rank. In addition, the Service.Rank interaction just achieves statistical significance at 5%, while that for differences between the genders is also significant at better than 5%.

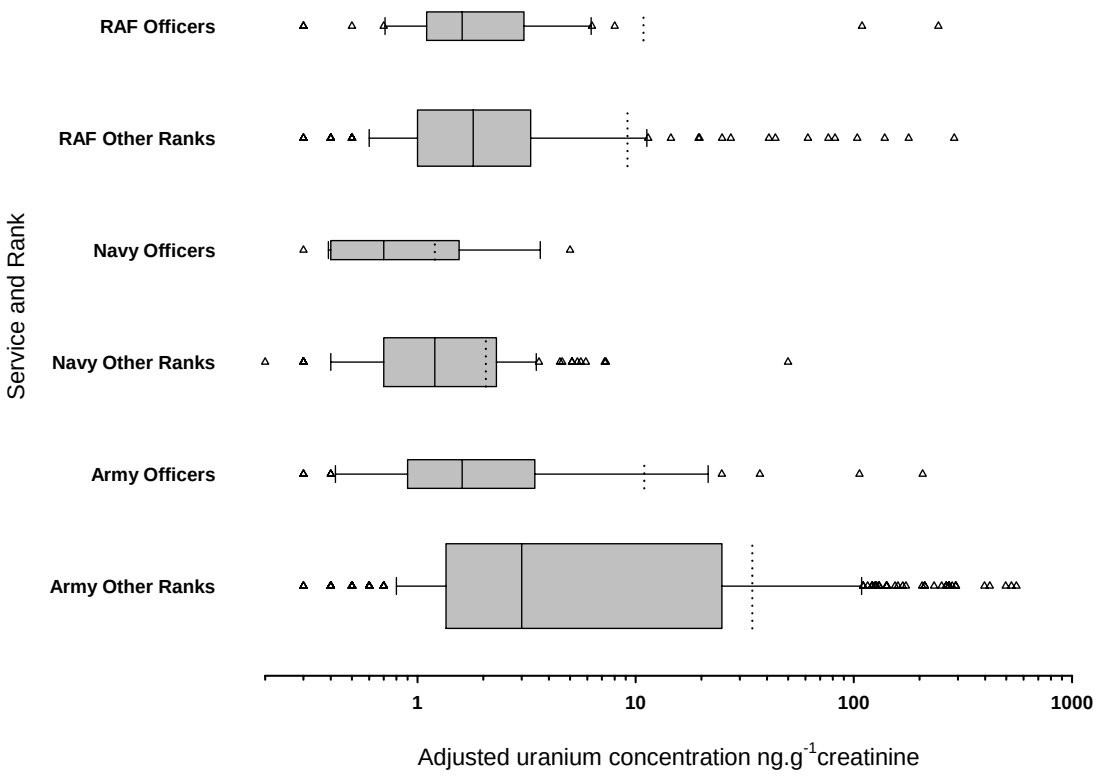

Figure 4.6 Boxplots of distributions of creatinine-adjusted uranium concentration by Service and rank

Figure 4.6 is a box-plot summarising the distributions of urinary uranium concentration adjusted for creatinine, for each combination of Service and rank. This figure again shows clearly the differences between the Services, and the differences between officers and other ranks within each Service. The Service.Rank interaction in the ANOVA table arises because the distributions for officers and other ranks in the RAF are rather closer than for the other two Services.

The estimated coefficient for the contrast between males and females was –0.492, which is interpreted as suggesting that, adjusted for Service and Rank, males had average creatinine-adjusted uranium concentrations only 61% of those in females.

4.4.4 Analysis of urinary creatinine concentrations

Table 4.7 is an ANOVA table summarising the results of sequentially fitting the factors to the logarithms of creatinine concentrations.

For creatinine, there are highly significant effects of Service and rank, plus a strong overall difference between the genders after adjustment for Service and rank. These systematic differences in the subjects' average creatinine concentrations help to explain why the results for unadjusted and adjusted uranium concentrations show different patterns of effects.

Table 4.6 Summary of Analysis of Variance (ANOVA): uranium concentration adjusted for creatinine (log scale).

Source of variation	d.f.	Mean Square	F-ratio
Service (Army, Navy, RAF)	2	129.57	53.06
Occupational Group (OG) (Combat, Support, Auxiliary)	2	0.28	0.12
Service.OG interactions	4	0.43	0.18
Rank (Officers, Other Ranks)	1	27.09	11.09
Service.Rank	2	7.32	3.00
Rank.OG	2	1.93	0.79
Service.Rank.OG	4	1.00	0.41
Gender	1	10.56	4.32
Service.gender	2	0.78	0.31
Residual	711	2.44	
Total	731	2.82	

Table 4.7 Summary of Analysis of Variance (ANOVA): creatinine concentration (log scale).

Source of variation	d.f.	Mean Square	F-ratio
Service (Army, Navy, RAF)	2	5.652	14.02
Occupational Group (OG) (Combat, Support, Auxiliary)	2	1.034	2.56
Service.OG interactions	4	0.921	2.28
Rank (Officers, Other Ranks)	1	3.176	7.88
Service.Rank	2	0.565	1.40
Rank.OG	2	0.296	0.73
Service.Rank.OG	4	0.976	2.42
Gender	1	7.281	18.06
Service.gender	2	0.493	1.22
Residual	711	0.403	
Total	731	0.439	

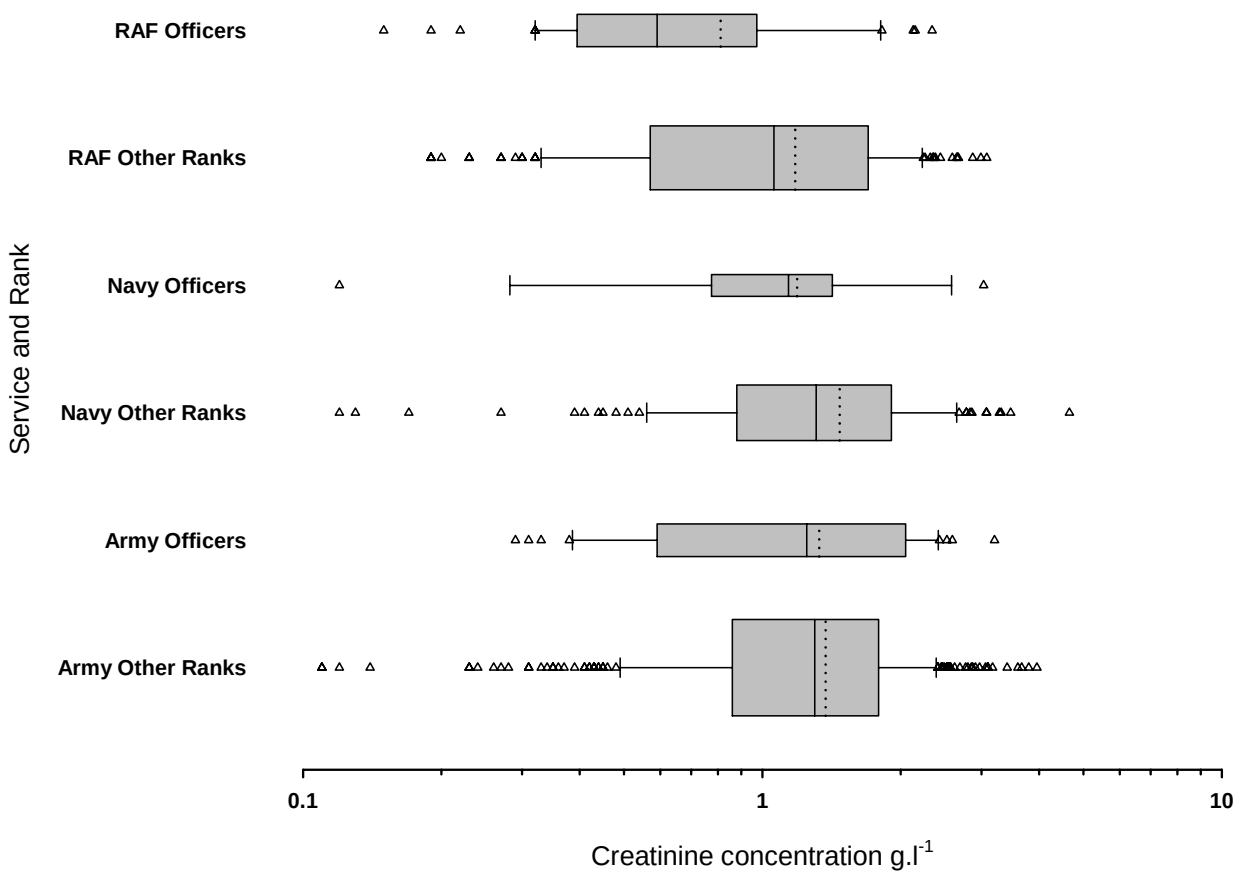

Figure 4.7 Boxplots of distributions of urinary creatinine concentration by Service and rank

Figure 4.7 is a box-plot summarising the distributions of urinary creatinine concentration, for each combination of Service and rank. This figure suggests that creatinine concentrations are largely similar between Officers and Other Ranks within the Army, are slightly different in the Navy, and are very different in the RAF.

The estimated coefficient for the contrast between males and females was 0.409, which is interpreted as suggesting that, adjusted for Service and Rank, males had average creatinine concentrations 51% higher than those in females.

4.4.5 Differences by gender

Figures 4.8 to 4.10 are boxplots showing the distributions of uranium and creatinine concentrations and creatinine-adjusted uranium, by gender, unadjusted for any other factors.

Figure 4.8 shows higher average uranium concentrations in males than in females. However, this difference is confounded with differences by Service and rank; in the ANOVA of Table 4.5, after adjustment for these factors, there was no evidence of a gender difference. Figure 4.9 suggest little gender difference in average levels of creatinine-adjusted uranium concentrations, but Table 4.6 shows a significant effect of gender once adjusted for Service and Rank. Finally, Figure 4.10 displays a very clear difference in the distributions of creatinine concentrations between the genders. Table 4.7 shows that, even adjusted for Service and rank effects, the between-gender effect in the creatinine-adjusted uranium concentrations is still very strong.

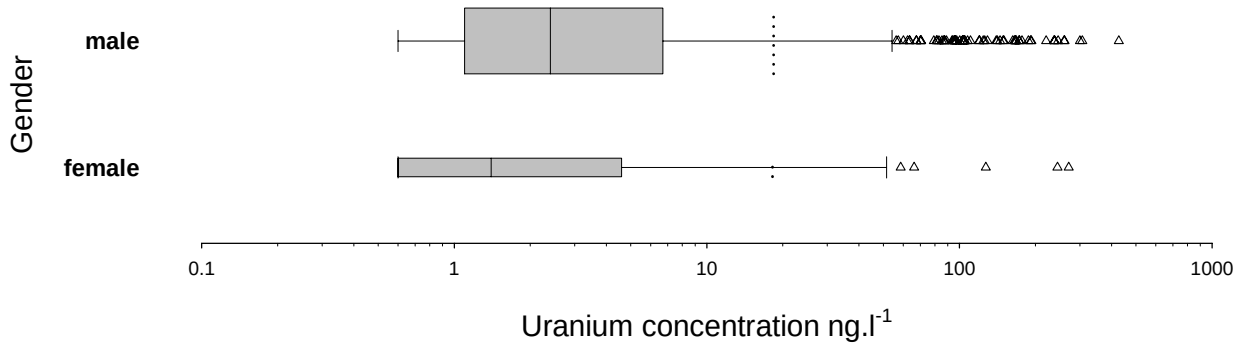

Figure 4.8 Boxplots of distributions of urinary uranium concentration by gender

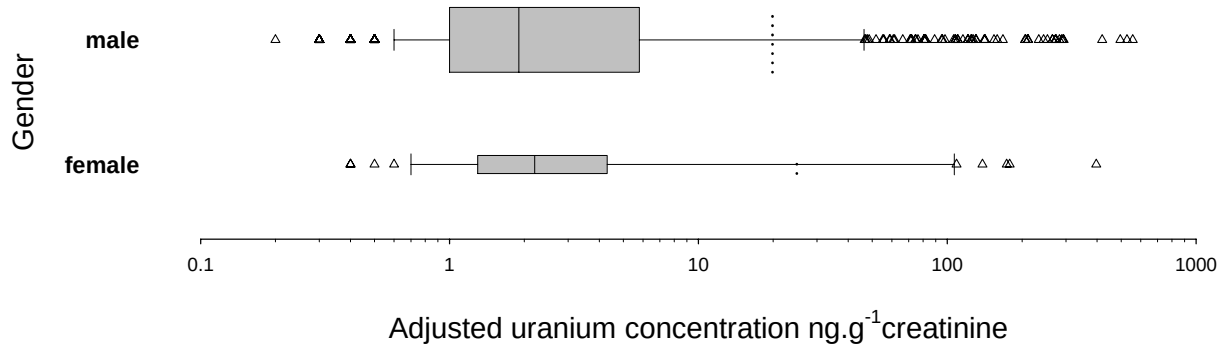

Figure 4.9 Boxplots of distributions of creatininine-adjusted uranium concentration by gender

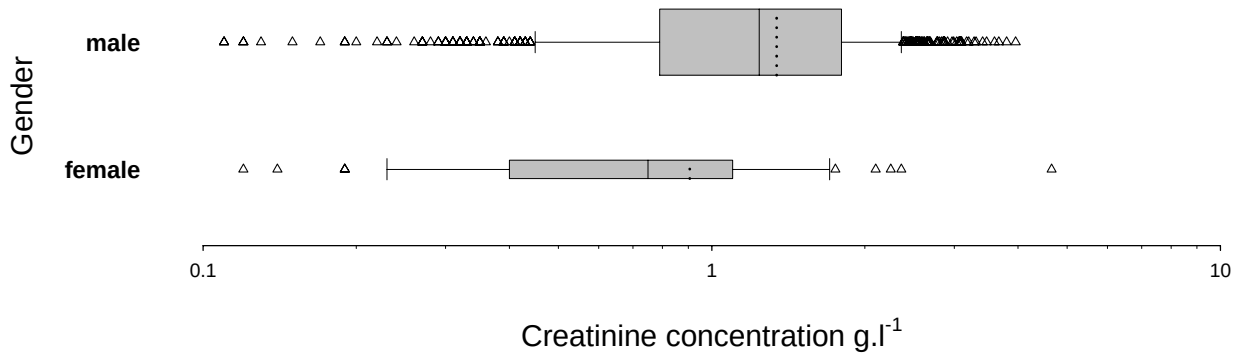

Figure 4.10 Boxplots of distributions of urinary creatinine concentration by gender

4.5 CHOICE OF REFERENCE DISTRIBUTION

The results above show differences in the average distributions of uranium concentration in urine, by Service and broad rank. It follows that a single reference distribution could be constructed in a number of ways, to represent the constitution of a chosen target population. What is ideal here will depend on what use is to be made of the reference, and particularly on whether individuals being tested for uranium are expected to come in equal or different proportions from the available numbers in the different combinations of Service and ranks.

For the moment, we propose that the combined distribution of Figure 4.1 is a potential reference distribution for the Forces as a whole. It has a preponderance of Army combatant other ranks, but then we may expect that those requiring testing for battlefield contamination are also likely to show such a preponderance.

It is plausible that testing would be almost entirely within this latter group, so another option would be to construct a reference distribution solely from Army other ranks, focussing on males. This is anyway the subgroup for which we have the most information. Noting that the ANOVA of Table 4.5 identifies no important role of occupational group, we propose that a distribution might be built from all the data for Army male other ranks, while noting that in any case combatants predominate in this group.

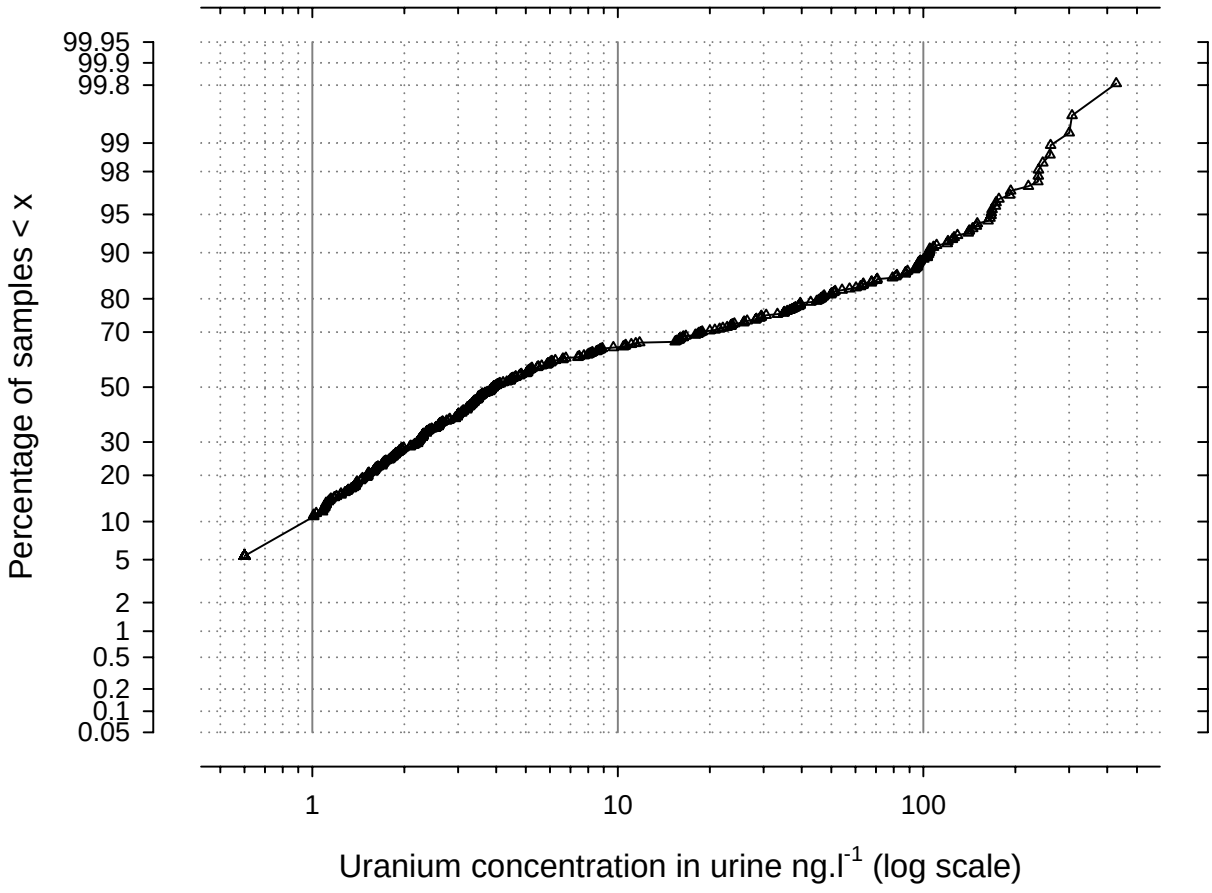

Figure 4.11 Lognormal probability plot of urinary uranium concentrations: Army male other ranks

Figure 4.11 shows the probability plot of this restricted group of 347 urinary uranium concentrations (corresponding to the boxplot labelled “Army Ranks” within Figure 4.5), of which 37 (10.7%) were values less than 1.0 with a notional value of 0.6. As expected, the whole distribution appears a little further to the right than that for the whole sample in Figure 4.7; as already seen, this group had the highest average concentrations.

The highest concentration recorded in Figure 4.11 was 427.6 $ng.l^{-1}$. The arithmetic mean was 31.5 (although this would change slightly if some value other than 0,6 were chosen to stand for <1.0). The median value was 3.9, and the upper percentiles were 29.5 at 75%, 104.4 at 90%, 166.6 at 95% and 260.6 at 99%.

Other reference distributions could readily be constructed by random sampling from the observed distributions, if it were desired to represent different combinations of Service and rank in the population to be compared

5 DISCUSSION

We have collected, and analysed the uranium content of, urine samples from 732 serving personnel from the British Forces. The subjects were selected to give a broadly representative mix of the Services and the types of occupations within them, and the selection took account of the known Forces-wide ratios of Officers to Other Ranks, and between genders.

Data on uranium concentrations in urine showed a range of values from below quantification limits to over 420 $ng.l^{-1}$. Important differences in distributions were observed between the Services, between Officers and Other Ranks, but not between genders after adjustment for these.

The concentrations of creatinine in urine differed by Service, and also between the genders after adjustment for other factors, men having on average higher rates of creatinine excretion. As a result, the creatinine-adjusted uranium concentrations showed less difference by Service than was seen in the unadjusted concentrations, and a small effect of gender. From Figure 4.5 it is clear that most of the values higher than 100 $ng.l^{-1}$ were concentrated in the Army Other Ranks.

Comparison of the highest values found here with ranges or reference values quoted elsewhere is complicated slightly by the fact that some authors quote uranium concentrations per litre of urine, while others quote only results standardised for creatinine; in the latter case, results may be quoted either per gm or per mol creatinine. It is possible to convert directly between the last two styles by observing that 1 g of creatinine is equivalent to 8.8 mmol (see section 3.5.4). Also, since the medians and means of the uranium concentrations unadjusted and adjusted (when expressed per gm of creatinine) in the present study were of similar magnitude, we may choose to convert between these on a rough 1:1 basis.

Various authors quote different values for reference ranges for urinary uranium concentrations. For example, Durakovic (2005) quotes a reference range terminating in a high value of 20 $ng.l^{-1}$, while McDiarmid *et al* (1999) recorded adjusted concentrations in Gulf War veterans not exposed to DU, up to 80 $ng.g^{-1}$ creatinine. Gwiazda *et* al, also in Gulf War veterans, recorded concentrations up to 40 $ng.g^{-1}$ creatinine. Ting (1999), in a study of 500 US residents, recorded a maximum concentration of 4080 $ng.l^{-1}$, with a 95^{th} percentile concentration of 34.5 $ng.l^{-1}$. Ough *et al*, studying Canadian veterans of the Gulf and Kosovo wars, found a maximum concentration of almost 50 $ng.l^{-1}$. The most comprehensive study of civilians, within the US NHANES study (CDC, 2005), recorded 95^{th} percentile values around 40 $ng.g^{-1}$ creatinine.

Compared with these values, we note that the 95^{th} percentile of 167 $ng.l^{-1}$ from the present study is somewhat higher, but that the maximum of 428 $ng.l^{-1}$ is lower than that found by Ting (1999). Overall, our values are broadly of the same order of magnitude as has been found elsewhere, if perhaps a little higher on average than in the USA.

These comparisons may be placed in context by studies of individuals in Finland drinking water from private wells drilled in granite (Karpas *et al*, 2005; Kurttio *et al*, 2002). These showed a range of concentrations an order of magnitude higher, up to 8,450 $ng.l^{-1}$, and a clear correlation with the estimated daily intake of uranium from well water (which in that region swamps the intake from other dietary sources). Durakovic (2005) reports on eight samples from residents of Afghanistan that also showed results of the order of 100 times higher than normal reference ranges.

It is important also to place these values in context with regard to health risks. Even at the highest concentration levels recorded in this study, no impact on health risks is expected; the radiation dosage would be negligible, and concentrations were orders of magnitude lower than Finnish subjects, in whom no symptoms of heavy metal poisoning were discernible (Kurttio *et al*, 2002).

With regard to comparisons between subgroups within the present study, the purpose of standardising for creatinine is to adjust for the dilution of urine, and in theory it should remove a source of variation in the raw uranium concentrations. However, the residual mean square for the adjusted concentrations (Table 4.6), which represents variation between individuals within subgroups, was slightly larger than for the unadjusted concentrations (Table 4.5); if we had removed a source of variation, we would have expected the residual to have decreased rather than increased. In our analysis of the pilot study of male civilian hospital patients, the comparable figures for variation between participants (Jones *et al*, 2005; Tables 5.6 and 5.7) reduced from 2.69 to 1.94 through standardisation. (We note that the residual mean squares in the present study are nevertheless of comparable magnitude to between-subject variation in the civilian pilot.)

To interpret these results, we observe that urinary creatinine concentration is determined by fluid intake and by body muscle mass, since creatinine is a product of muscle breakdown. Creatinine excretion is therefore a function of, amongst other things, the amount of muscle on an individual. In general, men have greater muscle mass than women, and average urinary creatinine concentrations in males tend to be higher than in females. In addition, we may expect differences in the extent of muscle development depending on the training requirements of different occupations, and these would work in such a way as to accentuate gender differences. If true, these would in turn affect raw comparisons between the Services and ranks, because these have different balances between the genders. In the present study, we may expect such differences to be accentuated, due to our intentional over-representation of army combat troops, who will have the highest level of physical training. All our findings are in line with these expectations.

It is therefore possible that adjustment for creatinine in this context over-adjusts, and it may be wise to place less reliance on adjustment within a study including both genders than in studies where subjects are more homogeneous than here. In our earlier civilian pilot study, all the subjects were males within a restricted age range (Jones *et al*, 2005). It has been suggested that testing for uranium in hair may offer an alternative to urine collection, removing the need to correct for urine strength (Karpas *et al*, 2005).

The method used here for determination of isotope ratio $^{238}U/^{235}U$ was developed for an operational requirement, within a surveillance scheme, to estimate a ratio where the urinary concentration lay above an action level of 30 $ng.l^{-1}$. In fact, the method was shown to provide a reliable ratio in most samples with a concentration down to 8 $ng.l^{-1}$, except in a few cases where matrix effects (other metallic elements present) reduced the precision of the estimate. Thus we had reliable isotope ratios only at the higher concentrations. However, all reliably measured ratios were consistent with uranium from natural sources, and we can therefore be confident that the upper percentiles of the distributions put forward as references represent uranium only from natural sources.

Uranium concentrations, whether raw or adjusted, showed clear and statistically significant differences in distribution between the Services, and between Officers and Other Ranks within each Service, with Army Other Ranks displaying the highest concentrations. Why there should be differences is not clear. Certainly, the explanation cannot lie with DU exposure during earlier conflicts: the natural isotope ratios preclude this. The answer may more plausibly lie in differences in diet, whether from food, water or other beverages. Bottled mineral water is likely to contain increased amounts of uranium, as will natural water within certain geological regions, particularly where water supplies are in contact with granite. However, we have no data on diet, nor on the residential history of our subjects, that would allow an analysis with regard to these factors. A reviewer has suggested that contamination from dust should be considered, since dust and soil, and even talcum powder, contain some uranium. However, the QC procedures included blanks and spiked controls, and no contamination was detected in any of these, so contamination within the laboratory seems an unlikely explanation, particularly where the difference in distributions seem so structured. It is possible that soldiers have higher inherent exposure to dust and soil, and may ingest more of these; if so, the observed distribution may be a legitimate reference for measurements in other soldiers.

Given that we do not have data with which to explain the observed differences, there remains the question of whether we should accommodate them in describing a reference distribution. Clearly, a distribution built from our Services data will have a different centre, depending on the proportions contributing to the distribution from each Service, and the ratios of Officers to Other Ranks (and possibly males to females). Once such a set of proportions is defined, we could build up theoretical distributions by stratifying our data set and randomly re-sampling the strata in the desired proportions. In this report, we have presented distributions of raw urinary uranium distributions for the whole of our data set, and for the single stratum comprising male Army Other Ranks.

6 ACKNOWLEDGEMENTS

We thank the Ministry of Defence for funding the study, and to civilian and Service experts for advice and encouragement.

We thank the volunteers who agreed to participate in the study. We are grateful to all of the serving staff in each of the Services who assisted in arranging access, appointments and facilities, and who helped during the site visits.

The analysis of the samples was undertaken by Cathryn Valentyne and Bill Leach at the Institute of Naval Medicine; logistics were handled by Cathryn Valentyne.

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APPENDIX 1: PROTOCOL APPROVED BY MINISTRY OF DEFENCE (NAVY) PERSONNEL RESEARCH ETHICS COMMITTEE

Institute of Occupational Medicine

DU Normative Value Study (Military): IOM Ethically Approved Protocol 20 February 2004 Tender No RD033-01074

1.1	**Project Title**	**DU Normative Value Study (Military)**
1.2	**Project Officer**	**Dr Andrew P Colvin, IOM**
1.3	**Associated Workers**	**Dr Colin Soutar, IOM** **Dr Brian Miller, IOM** **A Heather Tait, IOM** **Scott Dempsey, IOM** **Peter Hutchison, IOM**
1.4	**External Consultants**	**None**
1.5	**Independent Medical Officer**	**Wing Commander John Aitken**
1.6	**INM Task No.**	**RD033-01074**
1.7	**Customer Name**	**Ministry of Defence**
1.8	**Customer Code No.**	**RD033-01074**
1.9	**Tasking Reference**	**RD033-01074, 7/3/03**
1.10	**Establishments**	**Royal Navy, Army and RAF establishments**
1.11	**Location for Study**	**Tri-service bases as selected for inclusion**
1.12	**Experimental Dates**	**January to June 2004**

2 INTRODUCTION

IOM has been asked by Ministry of Defence (MoD) to design and undertake a cross-sectional survey of urine concentrations of depleted uranium in service personnel in the UK and Germany.

The MOD's Statement of Requirement is for the following:

- Design of a normative value study in conjunction with the MOD;
- Production of a protocol for the study;
- Obtaining ethical clearance for the study;
- The collection of the urine samples;
- The storage of the urine samples;
- Statistical analysis of the data and reporting;
- Publication of the work.

This research project has been prepared to meet these requirements, and makes proposals for a simple study design in response to discussions with MOD.

Background

There have been concerns expressed by some, with considerable media attention, about the potential health effects of exposure to depleted uranium following active service in war zones where depleted uranium has been used. A recent review by the Royal Society (2001) concluded that it was unlikely that any excess of fatal cancers from possible radiation effects would be detected in a cohort of 10 000 soldiers followed over 50 years and very few individuals were at risk of developing kidney disease. The lifetime risk of death from lung cancer in the most exposed individuals, however, might be double that of the general population and they could also be at risk of developing serious kidney disease in later life (a possible effect of uranium as a chemical). In addition, McDiarmid *et al* (2000) have found evidence of neurocognitive impairment in Gulf War veterans who had retained fragments of DU shrapnel, although these individuals showed little evidence of impaired kidney function. The Royal Society acknowledged that there was a great deal of uncertainty in their assessment of DU exposure and their recommendations included the need to validate the measurement of urinary DU concentrations as a measure of past exposure. Since the publication of the Royal Society Report, the MOD's DU Oversight Board has overseen a programme of development work.

The uranium content of urine in the general population is not well understood but is thought to vary considerably depending on where people live, their diet and their intake in drinking water. The use of DU is not confined to the military and some exposure to DU is likely to have occurred locally within the UK. The WHO (2001) reviewed data from the early 1990s that suggest that urinary uranium concentrations in the general population range from about 4 to 57 ng/l. Gulf War veterans known to have been exposed to DU are reported to have had urinary concentrations averaging 80 ng/l, 7 years post-exposure with the highest concentrations being about 30 000 ng/l (McDiarmid *et al*, 2000). Measurement methods have improved considerably over the last decade. A recent survey of uranium concentrations in the US population found that the median concentration was only 5 ng/g creatinine (7 ng/1), but 10% of the measured concentrations exceeded 24 ng/g creatinine (43 ng/l) (National Health and Nutrition Examination Survey, 1999). Measured concentrations did not fit a normal or log-normal distribution but had a marked tail at the higher end of the scale.

Given the ongoing concern about the potential effects of DU, the Ministry of Defence (MOD) has stated that biological monitoring for DU exposure will be available to any service personnel who have served in an area where DU has been, or may be, used. To support this commitment, MOD requires collection of a set of urine samples from service personnel (Navy, Army and Air Force) that can be used as a baseline for post-deployment testing, taking into account factors including occupation and location. The screening will include a urine test for uranium isotopes and total uranium.
The resulting information on the range and frequencies of depleted uranium and uranium urinary values in the military population could be used to:

- compare with those in an intended study of a civilian population;
- help to interpret the values that may be found clinically in individuals, including those who have fought in Iraq or Bosnia;
- permit future comparisons with those who are currently deployed in Iraq (note that this may imply a need for some supplementary sampling of selected groups, described later);
- facilitate case-control studies to investigate possible reasons for atypically high values.

The Institute of Occupational Medicine was invited to tender for this work, which is funded by the Ministry of Defence (ITT Reference No: RD033-01074. Issue Date 7 March 2003. Mr Wayne Lamport, Commercial Services, DSTL Farmborough) and co-ordinated by Mr Charles F Williams BSc MPhil (GVIU – Research A). The Project Officer and associated workers have no conflicts of interest to declare.

An additional summary of this project in lay language is given in the Subject Information Sheet at Annex A and Administrative Officer Information Sheet at Annex D.

This research project is being submitted solely and for the first time, to MoD(N) PREC for ethical approval.

3 AIM

The aim of this study is to characterise the overall distribution of values of urinary depleted uranium and uranium concentrations in military personnel in all three services.

4 METHODS

4.1 Design, Sample size and Early Stopping Rule

4.1.1 Fundamental Design and Sampling Strategy

The aim of the study is to describe the distribution of urine uranium and depleted uranium in the military population in general, excluding those who have recently served in Iraq and reservists. Those who have recently served in Iraq (Op-TELIC) will be subject of a separate screening programme. It is specifically required that the sample should include adequate numbers of front line personnel.

We propose to sample 1000 subjects on the basis that this number should be sufficient to describe the distribution of values across the sample. This is important since the focus of this study is to characterise the entire distribution including its extremes. More samples or a different sampling strategy would be required if precise estimates were required for the distribution of DU levels within different groups, or to compare the distributions across groups, but these are not objectives of the current project. Since no comparisons are intended, questions of statistical power are not relevant.

A simple random sample of the services would be impractical, because this could mean sampling at many bases/locations across the whole of Western Europe. In addition, our advice from DASA was that it would not be straightforward to arrange central access to the individual data that would be necessary. We therefore plan to organise cluster sampling, based on a few typical locations from each service. Within each sampling location, samples will be organised on a stratified basis to the extent possible, but in the knowledge that, in most cases, the data required for stratified sampling would likely be limited and would probably not be available in advance of site visits. These constraints have informed our current view of sampling procedures, which will be piloted and developed at selected locations as a first step in the study fieldwork.

By agreement with DASA, the steps in defining the samples are to be:

1. Specific locations to be chosen for each service
2. IOM to receive summary tabulations breaking down populations at chosen locations and elsewhere
3. Descriptive breakdowns to be stratified by chosen variables
4. Sample numbers to be designated within strata to construct a representative sample of the Service Population as a whole
5. IOM to liaise with local staff over procedures for invitation to attend voluntarily
6. Reject any with Op TELIC service or reservists

Because of the way that military personnel records are organised, and units are deployed to bases, the sampling will be stratified by:

1. Service; about 500 from the Army (including 50 from a Tank Unit), 300 from the Royal Air Force and 200 from the Navy (including 50 Royal Marines).
2. Location; potentially from ten locations, representing all three services, following discussion with MoD:

RAF	RAF Leuchars RAF Marham RAF Lyneham ***or*** RAF Brize Norton
Royal Navy	One or more operational ships Fleet Protection Group Royal Marines (FPG RM)
Army	Aldershot Catterick Colchester King's Royal Hussars (Tank unit) (KRH)

FPGRM and KRH are included specifically because they are front-line battle units. The choice between Lyneham and Brize Norton will be made on the basis of convenience, once contact is made with Commanding Officers. The sample chosen at each location will be stratified by gender and by rank (distinguishing officers from other ranks).

We want the sample to broadly representative of the various trades to which personnel are employed, and in particular to achieve a mix across three broadly defined occupational groups:

A. Infantry/ Armour;
B. Artillery/ Signals/ Engineering;
C. All other support and ancillary trades, e.g. Logistics, Transport, Medical, Dental, etc.

(as these would be interpreted for each service).

In the absence of information about individuals' trades, our initial assumption was that sampling could be arranged locally to give a reasonably representative mix across the three occupational groups. On the basis of information made available to us, however, this approach seems to be feasible only for the Navy and Air Force bases. The situation at the Army locations is different, in that typically there are several different and distinct units or regiments, for example front line regiments; (tanks, infantry), and other regiments, (engineers, artillery, signals, REME, transport, logistics, medical, dental and religious; (the last three relatively small) that essentially already make these occupational distinctions. Each unit manages its own lists of personnel, which are not always co-ordinated at location level. We therefore propose to sample at Army bases around a small number of units that will give a representation of typical occupations. Not all occupations can be sampled in this way, but we have no reason to expect that this method of sampling will introduce any bias with respect to the distribution of uranium burdens. This method is assisted by the fact that Army records can be used to exclude in advance whole units or individuals that have recently served in Iraq.

4.1.2 Early termination criteria

No rule will be applied in order to terminate the study early.

If this study is prematurely terminated for any other reason, MoD(N) PREC will be informed and provided with justification for the early termination.

4.2 Composition of study sample

The DASA branch for each service has now provided data on which to base sampling. The formats for each were different, so it is useful to consider each service individually.

Air Force

The advice we have been given is to base our sample on three locations: Leuchars, Marham and *one* of Lyneham or Brize Norton. (Choice between the last two may be made on considerations either of sampling or of convenience.)

Data were supplied in the form of summary tables for these four locations, stratified by various combinations of gender, trade, rank and age. Since we do not expect to be able to select by either age or trade, we show here a tabulation by gender and rank only.

While there are some variations, the overall impression was that numbers at the sites are quite similar; and the ratios officer:other rank and male:female also differed little. Other tabulations show that each site has a mix of trades and ages. For practical reasons therefore, we suggest that we take equal numbers from each site, with the same mix of genders and ranks. Once a choice is made between Brize Norton and Lyneham, we will have our required 300 subjects.

Table 1
Available subjects and sample for RAF

Site	Rank	Gender			Suggested sample		
		Male	Female	Total	Male	Female	Total
Leuchars	**Officer**	212	27	239	**18**	**2**	**20**
	Other	1421	115	1536	**72**	**8**	**80**
	Total	1633	142	1775	**90**	**10**	**100**
Marham	**Officer**	218	29	247	**18**	**2**	**20**
	Other	2217	228	2445	**72**	**8**	**80**
	Total	2435	257	2692	**90**	**10**	**100**
Brize Norton	**Officer**	341	47	388	**18**	**2**	**20**
	Other	2552	294	2846	**72**	**8**	**80**
	Total	2893	341	3234	**90**	**10**	**100**
Lyneham	**Officer**	418	57	475	**18**	**2**	**20**
	Other	1710	234	1944	**72**	**8**	**80**
	Total	2128	291	2419	**90**	**10**	**100**

Navy

For the bulk of the Navy sample (i.e. excluding RM), we intend to sample a ship-based population. This could be done by arranging a sampling visit to a ship when in port; alternatively, we could ask that the Navy transfer selected IOM staff on board a suitable ship for on-site sampling. To accommodate the sampling in the most practical way, arrangements will be finalised when the exact timing of the sampling is known. In either case, the principle of sample construction would be the same.

A particular sub-group of interest within the Navy is Royal Marine Commandos, because they are front-line troops. We have been informed that most commando units have in fact been deployed in Iraq, but that a few have not, including the Fleet Protection Group RM, based in Faslane, Scotland.

Table 2 shows the breakdown by rank and gender within FPGRM, and aboard HMS Invincible, as an example of a large operational ship. (Invincible has been suggested as a possible source of naval subjects; however, it may be necessary to base our sample on a similar pattern from a different ship(s), depending on deployment at the time of the survey).

Within HMS Invincible, there are about 20% female staff and 15% officers, and the suggested sample splits the target of 150 naval subjects in these proportions. The FPGRM are almost entirely male, and these have also been split by rank in the ratio 85:15 other ranks to officers.

Table 2
Available subjects and sample for Navy

Site	Rank	Gender			Suggested sample		
		Male	Female	Total	Male	Female	Total
HMS Invincible	**Officer**	97	15	112	**20**	**5**	**25**
	Other	516	133	649	**100**	**25**	**125**
	Total	613	148	761	**120**	**30**	**150**
FPGRM	**Officer**	27	0	27	**8**	**0**	**8**
	Other	453	1	454	**42**	**0**	**42**
	Total	480	1	481	**50**	**0**	**50**

Army

Data sent by DASA Army took a different form. Suggested sampling locations were Aldershot, Catterick and Colchester bases, but each of these houses a number of different units, of different specialism. It was also considered at an early meeting with MoD that it was important to include a tank unit, and data have been supplied for the Kings Royal Hussars. We propose to sample 50 subjects from KRH and 450 from the other Army specialities, as described below.

The data for the Army units at these locations have been supplied at a greater level of detail than for the other services, and subjects who served in Op TELIC have been explicitly excluded.

Since the Army data were classified by regiment, unit or corps, it has been possible to classify these in to the three broad occupational groups originally intended. Table 3 below shows the numbers in these groups at each base, broken down by gender and rank. The gender and rank ratios differ a little, but not significantly, and combining the three bases introduces no serious distortion. The ratio of other ranks to officers is about 10:1 overall. There are no females in Group A, and hardly any in B. In Group C, there are 129 females, which is about 3% of the total, so we propose to sample 3%*450 = (approx) 15 females. The male sample number 435, allocated for sampling across the groups in the observed ratio of 16:1:3.

Table 4 shows a similar breakdown for the KRH tank regiment. Here we propose to take 50 male subjects from Group A only, with an officer:ranks ratio of 1:10.

The sampling procedure for the three Army bases may need to be finalised in the field with the Administrative Officer and local liaison staff. On the assumption that identifying data and liaison for different corps may not be the same within a base, we propose to select specific corps as representative of their group, and sample by these.

Table 5 shows a breakdown of the available units/corps within each group at each base, by rank, and gender, on the basis of the data supplied. For Group A, we propose to concentrate our sampling effort on the largest of the units/corps within these groups. Thus, we will sample approximately equal numbers from some or all of the following corps:

Aldershot	POW, Footguards
Catterick	Kings Div, Scots Div
Colchester	Queens Div, Paras.

For Occupational Group B, we propose to take the sample entirely from Catterick, and for Occupational Group C, from Colchester. Suitable units, corps or regiments will be selected to represent these groups at each base. These choices reflect the relative strengths at the two bases, and are made for convenience and efficiency. They are unlikely to introduce any bias into the sampling.

We believe that the above sampling strategy will produce a range of subjects that will be representative of the Services as a whole.

Table 3
Available subjects and sample for Army

Site	Group	Rank	Gender			Suggested sample		
			Male	Female	Total	Male	Female	Total
Aldershot	A	Officer	89	0	89	**10**		**10**
		Other	1030	0	1030	**106**		**106**
		Total	1119	0	1119	**116**		**116**
	B	Officer	0	1	1			
		Other	44	1	45			
		Total	44	2	46			
	C	Officer	7	2	9			
		Other	63	25	88			
		Total	70	27	97			
Catterick	A	Officer	105	0	105	**10**		**10**
		Other	877	0	877	**106**		**106**
		Total	982	0	982	**116**		**116**
	B	Officer	8	0	8	**2**		**2**
		Other	116	2	118	**20**		**20**
		Total	124	2	126	**22**		**22**
	C	Officer	49	10	59			
		Other	220	37	257			
		Total	269	47	316			
Colchester	A	Officer	74	0	74	**10**		**10**
		Other	1097	0	1097	**106**		**106**
		Total	1171	0	1171	**116**		**116**
	B	Officer	1	0	1			
		Other	39	0	39			
		Total	40	0	40			
	C	Officer	30	9	39	**6**	**2**	**8**
		Other	315	46	361	**59**	**13**	**72**
		Total	345	55	400	**65**	**15**	**80**
3 Bases combined	A	Officer	268	0	268	**30**		**30**
		Other	3004	0	3004	**320**		**320**
		Total	3272	0	3272	**348**		**348**
	B	Officer	9	1	10	**2**		**2**
		Other	199	3	202	**20**		**20**
		Total	208	4	212	**22**		**22**
	C	Officer	86	21	107	**6**	**2**	**8**
		Other	598	108	706	**59**	**13**	**72**
		Total	684	129	813	**65**	**15**	**80**

Table 4
Available subjects and sample for tank regiment

Site	Group	Rank	Gender			Suggested sample		
			Male	Female	Total	Male	Female	Total
KRH	A	Officer	39	0	39	**5**		**5**
		Other	408	0	408	**45**		**45**
		Total	447	0	447	**50**		**50**
	B	Officer	2	1	3			
		Other	67	3	70			
		Total	69	4	73			
	C	Officer	2	2	4			
		Other	33	10	43			
		Total	35	12	47			

4.3 Exclusion criteria

Personnel who have recently served in Iraq on Operation TELIC will be excluded.

Service personnel will not be excluded if medically restricted. Pregnancy or lactation in serving female personnel will not be grounds for exclusion from the Study.

Reservists are excluded from the study since their lifestyle might not be representative of the British military population in general.

Only serving personnel stationed in the UK and western Europe will be sampled due to practical reasons. IOM staff will elicit the above information by questionnaire prior to urine collection and those who do not meet the criteria above will be excluded from the Study. See Annex C for a copy of the initial questionnaire. In cases of doubt as to whether an exclusion criterion is present or not, subjects will be excluded.

4.4 Procedures

4.4.1 Outline

Initially the Principal Personnel Officer (PPO) of each service will be requested via MoD channels for authorisation for the study to proceed (IOM having previously obtained high-level MoD authority). The PPO will contact the Commanding Officer of selected units/bases at each selected location requesting the appointment of a local 'Administrative Officer' with whom IOM could liaise. IOM will then deal directly with the local Administrative Officer of the selected military sites in order to arrange briefing and initial contact with potential volunteers. The PPO will be provided with a Study Protocol once ethical approval had been obtained and will be appropriately briefed by letter and telephone by IOM clinical staff.

IOM, with MoD assistance will have carefully selected ten location sites (two Royal Navy, five Army and three RAF) which are representative of each of the services overall in terms of military population. Within each location site, individual units will also be selected carefully in order to define the desired overall population sample, which will be representative of the services as a whole in terms of gender, rank and occupational group/unit. So far only infantry (Group A) selected from the Army.

The required numbers of servicemen/women will be drawn up according to the above sampling strategy. Individuals will be randomly selected from volunteers within the identified units at the

selected locations after an appropriate initial briefing and information sheet has been presented to them by the Administrative Officer and/or IOM clinical staff. This written information explains the purpose and nature of the study, and provides the basis for informed consent by the subject. A record of personal data including gender, age, rank, length of service, unit/branch/corps, a brief history of previous deployment and current medical fitness category will be taken by self-administered questionnaire under the supervision of IOM clinical staff.

The Administrative Officer at each location will explain the purpose and nature of the study at unit level with assistance from IOM staff as required. The Commanding Officer will ensure that volunteers are available to participate in the study. IOM will provide all letters, information sheets and forms as attached at Annexes A, B, C and D.

Volunteer subjects will complete the forms with assistance from IOM clinical staff, who will then supervise the collection of the urine sample using a standard protocol. The answers to the questionnaire will be recorded and later computerised. The urine samples will be refrigerated and sent back to IOM or INM as described below.

In order to minimise the risks of sample degradation through poor or inappropriate treatment, a protocol has been developed in close collaboration with the INM laboratory where the analyses are to be undertaken. This includes the following:

1. IOM stores and transports the urine samples in tamper evident sealed bags at 0° to 4° C and processes the data.
2. IOM passes the urine samples on to the laboratory of the INM in secured containers.
3. INM analyses the urine uranium isotope ratio and passes the results back to IOM.
4. IOM analyses the results, consulting with INM and drafts the report.
5. IOM reviews whether the sample population is adequate and representative, and makes proposals accordingly.
6. During the statistical analysis IOM identifies subjects in higher risk trades who previously saw active service in the Balkans or the Middle East (excluding Op TELIC), and describes them separately from the analysis of the "normal" military population.
7. If any group were to be studied specifically, this will be the time to consider whether the group is large enough to permit statistically significant comparisons, or whether additional recruitment is required. This work is not included at present in this protocol.

There may be practical difficulties that make it difficult to follow this plan exactly at each collection site. Procedures will be defined in discussion with each Administrative Officer, to enable realisation of the key principles within practical constraints. Note that the above may not correspond to date order.

4.4.2 Detailed description

Sample collection

IOM will arrange for the collection of urine samples and questionnaires from the specified number of individuals at locations agreed with the MOD during the study design process. It is assumed that MOD will provide nursing support for taking urine samples from female subjects. A short information sheet on the study that the local Administrative Officer will be able to use in their recruitment of volunteers is provided at Annex D.

An experienced member or members of IOM's medical team will supervise the collection of a minimum of 100 ml freshly voided urine samples from military personnel. A maximum sample quantity will be specified to prevent leakage from the sample bottle during cold storage (freezing). Midstream specimens of urine or other special anti-contamination procedures are not considered

necessary by IMN Analytical Laboratory staff. Nor is any immediate urine sample preparation required. Details of the IOM staff will be supplied to and approved by the MoD prior to the sample collection. The clinical supervision will include:

- briefing the study subjects on the purpose of the study, obtaining signed consent from the subject and administering the personal data questionnaire;
- information on the importance of adequate oral fluids before the collection starts.
- briefing the study subjects on how to give the sample, particularly with regard to avoiding sample contamination (MoD nursing assistance is requested for obtaining samples from female personnel).

The MOD have agreed to provide appropriate facilities (e.g. a medical room and nursing support) at each base for IOM's use on the days that sample collection is to be carried out. Local administrative support will be organised by the appointed location Administrative Officer.

Following collection, samples will be refrigerated. They will be transported back to either INM laboratory or IOM headquarters in Edinburgh at a temperature of 0° C to 4° C and transferred to a freezer as soon as is practicable after sample collection prior to laboratory analysis. Samples held at IOM headquarters will be stored no longer than five days before transfer to INM laboratory.

Sample containers

The sample bottles, collection funnels and containers used for storage and transport of the samples will be supplied by the analytical laboratory at the Institute of Naval Medicine. The sample bottles and collection funnels are to be composed of low density polyethylene. The Institute of Naval Medicine has run tests on a representative number of sample bottles from each batch used and have found no evidence that the bottles either leach uranium into or remove uranium out from the sample. The sample bottles will have been labelled by INM with a unique number and provided with an identically numbered form.

The sample bottles will be labelled and put in an individual sealed 'tamper evident' plastic bag following collection. They will then be secured in a locked container during transport.

The containers are likely to be suitable for use as supplied by the manufacturer, and will be provided by the Institute of Naval Medicine before sample collection is undertaken. The sample bottles will be cold packed using normal ice packs to maintain a temperature of 0° to 4° C during transport.

Sample storage

During the collection phase the samples will be placed in a fridge at 0° to 4° C before being transferred to INM with ice packs to maintain a temperature of 0° to 4° C.

IOM and/or INM will freeze the samples and store the frozen samples until analysis is complete up to two years after collection. After two years, or earlier by agreement with MoD, the samples will be disposed of as clinical waste. It is unlikely that long-term storage of the samples will affect the creatinine content of samples. Urine samples are routinely stored for periods of weeks to months without serious degradation, however, it is not possible to be certain that no degradation will occur over two years. Samples will be protected from defrosting since repeated re-freezing could conceivably affect creatinine contents.

IOM will make any samples held available to the MOD on request. (MOD will arrange for the collection of the samples with another agency.) However it is anticipated that most, if not all, samples will be sent directly to the INM laboratory following collection.

Staffing

This contract will be primarily undertaken within IOM's Medical Division and the Director of Clinical Services, Dr Andrew Colvin, has overall responsibility for this work. Scott Dempsey, a senior occupational health technician and Heather Tait, a senior occupational health nurse are the staff most likely to be involved in the supervision of sample collection and the transport of samples back to Edinburgh (if required). The storage of the samples and the arrangements for any chemical treatment required at IOM will be the responsibility of the IOM Analytical Laboratory, under the direction of Dr Alison Searl, the Director of Analytical Services until handed to INM. Dr Brian Miller (Senior Statistician at IOM and Director of Research Operations) has advised Drs Colvin and Searl with respect to the development of the sampling strategy (with assistance from MoD), the conduct of the analysis and reporting. Dr Colin Soutar, Chief Executive and medical epidemiologist will provide supervision and support.

Foreign research workers

No foreign research workers will be employed on this contract.

Quality assurance

IOM is committed to providing high quality services. Research studies are conducted by project leaders with multidisciplinary teams. Detailed project plans are completed and approved before the project starts, and the project is conducted with frequent project meetings in which each member of the project team contributes expertise. Regular project reviews are conducted by senior staff. Draft reports and final reports are reviewed in house by senior staff and revised accordingly. Clients are kept informed of the progress of the project, and may be closely involved in the overview of the progress of the work if desired. Papers describing the work are subsequently prepared for the peer review literature, demonstrating that the work is conducted to a high standard. Draft reports are submitted to clients for comment before finalising. On the Consultancies side we have UKAS accreditation for a wide range of laboratory analysis, occupational hygiene sampling and asbestos work. Our staff are accustomed to working within quality systems. For all work, whether formally accredited by UKAS or not, we ensure that staff are properly trained for the tasks to be undertaken, that there are written instructions and that the staff involved have read and understood instructions and that proper records are kept. We have an internal audit system to ensure that the highest standards of quality are met.

Timescale

Subject to ethical approval, and on obtaining informed consent, and on the basis of collection of a total of 1000 samples from ten locations, it is intended that samples will be collected as soon as possible following contract placement (target date: late January 2004). This assumes that IOM experiences no difficulties in arranging dates and locations of sample collection with the MOD and that sufficient volunteers are available to provide samples on the agreed dates at each location, and that ethical approval can be obtained promptly. Subsequent data processing can proceed while the samples are being analysed by INM. It is anticipated that the statistical analysis, and reporting (in draft) can be completed six months after all the urine sample results have been collected.

4.4.3 Withdrawal criteria

Subjects will stop on attaining the first of the following criteria:

(a) on the request of the subject;
(b) on the instruction of the Independent Medical Officer;
(c) on the decision of the Administrative Officer or IOM clinical staff;
(d) if the volunteer is unable to provide a urine sample within a practical timescale at the time of collection.

4.5 Measurements

Personal data needed for each individual by questionnaire includes:

- full name;
- gender;
- rank;
- date of birth;
- date, time and location of sample collection;
- age of joining services;
- branch/corps/unit or occupational group;
- any previous active service in the Balkans or in the Middle East;
- medical fitness category.

Laboratory analysis will be undertaken by INM for total urinary uranium contents and for the isotopic ratio of the uranium present and creatinine. Results will be reported in terms of total uranium and isotopic ratio of U235 and U238 in urine, scaled relative to creatinine. It is anticipated that the total uranium content of a substantial proportion of samples is likely to be at or below the limits of detection which for the INM laboratory is 1.9 ng/litre. The analysis is theoretically subject to interferences from mercury chloride or mercury argon compounds which have similar masses to U235 and U238 respectively. Some individuals may have relatively high levels of mercury in urine as a result of dietary exposure (fish) and exposure to mercury in dental amalgam. No analysis for mercury has been planned at this stage, but it may be considered later as part of laboratory quality control procedures. The records received will be assumed to be complete and accurate.

4.6 Data analysis

Data protection and control

IOM will be Data Controller under the Data Protection Act, and has many years of experience in handling confidential research data. No individual study participants will be identified in the report.

Data processing

Questionnaire data will be entered to computer file. Data will be double entered with all discrepancies checked and verified. Appropriate procedures will be designed and implemented to check the collected data for logical consistency, valid values, valid ranges and cross record consistency.

The study subject's names and service number will be held separately along with the IOM's study subject identity number will be held separately in an Access database that will use the standard security model and include data encryption. The main analysis file will also be created in Access database format and will only identify subjects using the IOM's study subject identity number. This database will be subject to standard IOM IT security policies, which include security restrictions that ensure that only project team members would have access to these data. These measures ensure acceptable levels of data anonymisation.

The analytical laboratory of the Institute of Naval Medicine will provide the urine test results electronically in a form to be agreed during the study. Care will be taken to ensure a consistency in labelling the sample results so that they can be matched to the questionnaire data using a unique subject identifier. Urine test results will be checked and validated by INM before they are sent to the IOM.

On receipt of the data, IOM will construct a computer file system using Microsoft Access which links the personal data, questionnaire data and urine test results for each participant in the survey. All data in the database will be checked for completeness, consistency and validity before a fully anonymised file is produced for use in the statistical analysis.

All of the study data files will be stored on a *Compaq* Server on the IOM's network. The server is located in a secure, climate controlled computer room into which physical access is controlled and limited to IT administration staff. The IOM's IT Security Policies include issues of data security and the integrity of all computerised data. These procedures include a daily, full backup procedure, active protection from the threat of computer virus and prevention of unauthorised access to any study data. The study will run in full compliance with the Data Protection Act.

Any issues involving the data collection, data processing and systems design will be under the control of the project's systems analyst who will also review any other data related issues as appropriate to the requirements of the project.

Statistical analyses

The results will be anonymous, and no individuals will be identifiable in the reports. Results from the urine tests will be described for the population as whole and subdivided by service, rank, gender, location and broad occupational group. The distribution of the test results will be described and summary measures such as the mean, variability and inter-quartile range of the measurements will be calculated. Correlations between the total uranium and DU content of the urine will be calculated.

Associations between the uranium and DU measurements and factors such as age, gender, location, occupational group, unit, length of service and rank will be investigated using standard multiple regression methods. If necessary, the data will be transformed before use in the statistical analysis, for example by using the logarithm of the measurements.

Personnel in the Institute of Naval Medicine will be invited to comment on the design and results of the statistical analyses as they may beneficially be influenced by knowledge of the technical aspects of the measurements and the scientific context.

4.7 Reporting

The report, in the form of an IOM Research Report, will include a brief executive summary, a scientific summary, introduction, methods, results and discussion. Personnel in the Institute of Naval Medicine will be invited to contribute to the authorship of the report. A draft will be submitted to MOD for comment before finalising. IOM will take these into account, but will retain final editorial control. To demonstrate openly the independence of the study, the contract will stipulate IOM freedom to publish. IOM Research Reports are publications with a small circulation, and are

available on request. In addition, the work will be prepared for submission in due course to a peer-review scientific journal.

A copy of the principal report(s) covering this work will be submitted to the Secretary of MoD(N) PREC on publication.

It is not planned to routinely release individual results, but it is a requirement under the Data Protection Act to release individual information if requested in writing by individual study subjects. This will be complied with provided the true cost of supplying the information to the study subject by IOM is met prior to disclosure.

5. MEDICAL AND ETHICAL CONSIDERATIONS

IOM will obtain ethical clearance for the study by submitting a study protocol to the MOD (N) Personnel Research Ethics Committee for scrutiny and ethical approval. The study will observe and comply with all the limitations defined in the Schedule of Approved Procedures as issued by the Ministry of Defence (Navy) Personnel Research Ethics Committee.

Each volunteer will be invited to sign a consent form having been given adequate time to consider their decision to volunteer. Individuals will be provided with information by a printed information sheet and given the opportunity to ask questions of a member of the study team (either in person or by telephone). A copy of the subject information sheet and consent form will be included with the protocol submitted for ethical approval.

5.1 Medical cover

IOM staff will supervise the collection and transport of urine samples. The project leader, Dr AP Colvin will be on call by telephone as a source of advice or guidance to volunteer subjects, IOM clinical staff and to the local Administrative Officers during the study. Wing Commander Aitken will be on call for advice and guidance to study participants if required by telephone before, during and after the study sample collection phase.

5.2 Withdrawal criteria

Withdrawal criteria will be as previously written in Paragraph 5.4.

5.3 Compliance

This study complies, and at all times will comply, with the Declaration of Helsinki, as adopted at the 52nd WMA General Assembly, Edinburgh, October 2000, and with the Draft Additional Protocol to the Council of Europe Convention on Human Rights and Biomedicine on Biomedical Research (CGBI/INF (2001) 5 dated 18 July 2001).

5.4 Compensation

All subjects will enjoy the benefits provided by the MoD extant no-fault compensation scheme, and will be fully informed of that scheme and provided with written details.

5.5 Abnormal findings

If abnormal results are found then study participants and the independent medical officer will be informed in writing. No results will be passed to any other parties without specific written consent from study participants.

6. HAZARDS TO SUBJECT SAFETY

6.1 Electrical safety

No monitoring or other electrical equipment is connected to subjects.

6.2 Adverse effects

There are no significant adverse affects or health and safety risks that are anticipated from this research project.

6.3 Risk assessment

Assessment of the risks for this study lead to the conclusion that the risks are minimal given the innocuous nature of the project and the fact that only anonymised or group results will be routinely released.

If it becomes apparent during the course of the study that this assessment of risk changes in any way, MoD(N) and those participating will be informed fully and without delay.

6.4 Pregnancy and lactation

No measures to exclude potentially pregnant women are anticipated as being required.

7. SUBJECT PAYMENTS

In view of the innocuous nature of the trial, no subject payments are proposed.

8. REFERENCES

About the IOM

The IOM employs over 100 staff, most of whom are employed in our Edinburgh office. IOM was founded as a charity in 1969 by the UK coal industry in conjunction with the University of Edinburgh and our first major research programme on coalminers' lung diseases soon became a benchmark for studies in occupational epidemiology and hygiene. Over the next 20 years the IOM's applied research work spanned other industries (asbestos, chemicals, steel, textiles, construction) and other conditions (back pain, ULD, hearing loss) as well as extending into many areas of basic research, and in 1990 the Institute became a fully independent charitable organisation with its own Board of Governors. We have continued to develop our activities, focusing always on the expanding UK and international needs for independent high quality research in occupational and environmental health, hygiene and safety. In addition to our links with Edinburgh University, we have thriving links with the Universities of Aberdeen, Heriot-Watt and Napier. Since independence we have developed a rapidly expanding consultancy business (IOM Consulting) that provides a wide range of services in occupational health and hygiene, environmental consultancy, ergonomics, occupational psychology, and chemical analysis.

The Health and Safety Executive is our biggest single client and we have also undertaken a number of projects for the Department of Health, the Scottish Executive and the Department for International Development and its predecessor, the Overseas Development Agency. IOM scientists are members of the EPAQS, the Department of Health's Committee on the Medical Effects of Air Pollutants (COMEAP), the HSE Advisory Committee on Toxic Substances (ACTS), the HSE Advisory Committee on Pesticides (ACP) and the HSE Pesticides Incidents Appraisal Panel. IOM staff are actively involved in the HSE's "securing health together" programme.

About the INM Laboratory

The Occupational and Environmental Science Laboratory at the Institute of Naval Medicine has over twenty years experience of trace metal analysis in body fluid samples, principally blood and urine. The laboratory is UKAS accredited for both testing (lab no 2117) and calibration (lab no 0638) and is a member of a range of external quality assurance schemes for metals in blood, water and urine..

The laboratory is equipped with a range of trace metals analysis equipment including AAS, ICPOES and ICPMS. All uranium analysis is carried out by quadrupole ICPMS using either a Perkin Elmer Elan 6100 (total uranium) or a Perkin Elmer Elan DRC (isotopes). All analysis is carried out by graduate analysts with 5+ years experience of trace metal analysis and the use of ICPMS.

The method used for measurement of total uranium was developed in house based on published methodology and uses flow injection sample introduction and can accurately measure total uranium, based on ^{238}U, down to a concentration of 1.5 ng/l with a theoretical detection limit of 0.06 ng/l. Prior to analysis a rigorous instrument optimisation procedure is followed which is confirmed with system suitability checks. The analysis itself includes the analysis of three certified EQA samples at concentrations equivalent to 10, 50 and 90% of the calibration range. No data is released until the EQA data has been plotted on Shewhart control charts and shown to be acceptable. Three separate charts are maintained, one for each EQA sample, and data is accepted if it is within +/-2 SD of the target value based on the method validation data. Bias and drift are also monitored. Creatinine determinations are also carried out on each urine sample using an accredited method based on the Jaffe reaction. All data is expressed as uranium concentration in ng/l and as a uranium creatinine ratio in ng Uranium per gramme of creatinine.

The uranium isotope method, also developed in house, is based on the use of a quadrapole ICPMS with a dynamic reaction cell to control matrix effects. The method determines ^{235}U and ^{238}U but not ^{234}U and ^{236}U, which are present at concentrations too low for the instrument to measure. This however is reasonable as depleted uranium is by definition deficient in ^{235}U. The urine sample is analysed directly with no pre-treatment although acidification and/or microwave digestions could be used if a sample is heavily precipitated. The method has been fully developed and is capable of accurate isotopic measurements down to at least 6 ng/l for a sample with a depletion equivalent to 0.2% 235U. Final validation of the method will be carried out on receipt of certified reference materials from IRMM in Belgium. This will consist of a full statistical analysis of the precision and accuracy of the isotope determination and will allow mass discrimination effects to be controlled. The method will be accredited before use and preliminary discussions with UKAS lead us to believe that this will not be a problem. In routine use the method will be controlled by the inclusion of regular certified quality control samples at a range of isotope ratios. Again the resultant data will be assessed by means of Shewhart control charts prior to release of sample data. The data collected will also be reprocessed to generate concentration data which will be used to cross check the initial concentration data.

References

INM's Procedures for the Independent Medical Officer, EMU (1999).

Ministry of Defence (Navy), Personnel Research Ethics Committee. Administrative Guidelines for Ethical Approval and Conduct of Non-Clinical Research Conducted on Human Volunteers (The Schedule of Approved Procedures). June 2002.

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National Health and Nutrition Examination Survey (1999) US National Centre for Environmental Health. www.cdc.gov/nceh/dls/report/results/uranium

The Royal Society (2001) The health effects of depleted uranium munitions, Parts I and II. The Royal Society London (available from their website)

World Health Organisation, Department of Protection of the Human Environment, "Depleted Uranium: Sources, Exposure and Health Effects," Geneva, Switzerland, April 2000

Dr Andrew Colvin

Director of Clinical Services, IOM

Normative DU (Military) Study Project Leader

17 February 2004

ANNEX A: IOM Subject Information Sheet

Depleted Uranium Urinary Normative Value Study (Military)

You are asked to read this form carefully. A study is being conducted by the Institute of Occupational Medicine, an independent research organisation. If you consent to take part, you should sign the consent form. If you have any query, or are unsure about anything, you should not sign until your problem has been resolved and you are willing to volunteer. Please feel free to contact either the Project Leader or Independent Medical Officer (details overleaf).

Dear (name)

You probably know that questions have been raised about possible health effects of depleted uranium. We are asking you to volunteer for a study that is intended to find out what are the normal amounts of uranium and depleted uranium in the urine of personnel from the Royal Navy, Army and Royal Air Force.

The results will be used to compare with civilians and with military personnel who have been deployed recently in Iraq.

If you agree to participate, you will be asked to provide a specimen of urine, and answer a few simple questions on age, rank and history of active service.

No special arrangements or precautions are required before the urine collection. If you have any medical or other condition that may affect your fitness to take part in this study, please inform the IOM nurse/technician.

The urine collection and questionnaires will be supervised by Institute of Occupational Medicine clinical staff. Thereafter the samples will be analysed by the Institute of Naval Medicine for total uranium and isotopic ratio of uranium. Urinary creatinine will also be analysed to allow standardisation for fluid intake. It is possible that we might contact you through normal military channels at a later date, to ask for further information or samples.

Your results will be completely confidential, and will be used only for the purposes of health research. They will not be released to anyone without your consent. No individuals will be identified in the report. Urine samples will be disposed of as clinical waste after two years or earlier by agreement with MoD.

Taking part is entirely voluntary. There is no direct health benefit to the service personnel who take part and the test will not provide any information about the personal health of participants. The study is about protecting health in future and it will be better if most people do take part. People can decline, or withdraw at any time, or refuse to answer particular questions, without giving a reason.

I do hope you will agree to participate.

Yours faithfully

Dr Andrew Colvin
Institute of Occupational Medicine
Project Officer

Additional details

You have a right to obtain copies of all papers, reports, transcripts, summaries and other material so published or presented, on request to the Administrative Officer. All information will be subject to the conditions of the Data Protection Act 1984 and subsequent statutory instruments.

Experimental records, including paper records and computer files, will be held for a minimum of 30 years, in conditions appropriate for the storage of personal information. You have right of access to your records at any time.

The study has been approved by the Ministry of Defence (Navy) Personnel Research Ethics Committee. This protocol complies with all current legislation, including the Draft Additional Protocol to the Council of Europe Convention on Human Rights and Biomedicine Research (CDBI/INF (2001) 5 dated 18 July 2001). Further details of the approval will be provided if you wish, and you have a right to have a copy of the full protocol to retain, if you so request, of the Administrative Officer.

Project Leader: Dr Andrew P Colvin
Institute of Occupational Medicine
Research Park North
Riccarton
Edinburgh
EH14 4AP
Telephone 0870 850 5131
Mobile 07811 165513

Independent Medical Officer: Wing Commander John Aitken
Staff Officer Occupational Medicine
Defence Medical Services Department
0207 218 3619

ANNEX B: IOM Subject Consent Form

Depleted Uranium Urinary Normative Value Study (Military)

1. I have read the information sheet, which provides an outline of this study, and have had the opportunity to raise and discuss any questions with the Administrative Officer and the Independent Medical Officer, with regard to the general nature, object, potential risks and duration of the study, and understand what is expected of me.
2. I understand that in the event of my sustaining injury, illness or death as a result of participating as a volunteer in MoD research, I or my dependents may enter a claim with the Ministry of Defence for compensation under the provisions of the no-fault compensation scheme, details of which are attached. Such a scheme does not require me or my dependents to establish negligence on the part of the Ministry of Defence or its employees. I also understand that should such injury, illness or death have been caused by the negligence of the Ministry of Defence or its employees either I or my dependents may have a claim in law.
3. I understand that the aim of this study is to characterise the normal values of urinary depleted uranium and uranium concentrations in military personnel in the three services.
4. I agree to volunteer as a subject for the study described in the information sheet. I give my full consent to my participation in this study. I understand that my urine sample will be tested for creatinine, total uranium and isotopic ratio of uranium.
5. I understand that if abnormal results are found then I and the independent medical officer will be informed in writing. No results will be passed to any other parties without my specific written consent. I agree that I may be contacted directly by a member of the IOM Research Team if any further information is required, or to request further urine samples. This does not imply any agreement to any further study participation.
6. This consent is specific to the particular test described in the information sheet attached, and shall not be taken to imply my consent to participate in any subsequent experiment or deviation from that detailed here.
7. I reserve the right to withdraw from this experiment at any time; I also understand that I may be withdrawn at any time, and will suffer no penalty as a result.

Signed _____

Name _____ Date _____

Witnessed _____

Name _____ Date _____

Project Leader: Dr Andrew P Colvin
Institute of Occupational Medicine
Research Park North
Riccarton
Edinburgh
EH14 4AP
Telephone 0870 850 5131
Mobile 07811 165513

Independent Medical Officer: Wing Commander John Aitken
Defence Medical Services Department
Assistant Director of Clinical Policy
0207 217 8761

Institute of Occupational Medicine

ANNEX C: SUBJECT QUESTIONNAIRE

D.U. NORMATIVE VALUE STUDY

INTRODUCTION

The IOM is an independent centre of research. We have been asked by the Ministry of Defence to look at Depleted Uranium (D.U.) levels in the population of the tri-services within the UK.

Any information we collect will be strictly confidential and no names or other identifying information will be published or released to the M.O.D.

INSTRUCTIONS

Please complete the questionnaire on the other side of this page and hand it back to the IOM nurse or technician. Please ask if you require any assistance to complete the questionnaire.

1. Some of the questions have a list of possible answers with a box printed beside each one.

   Please choose your answer and put a tick in the box beside it, for example:

   Male ☑

   Female ☐

2 Some of the questions have boxes for you to write your answer in.

IOM Study ID number	

Unit location:	
Todays Date: / / 2004	Time of collection:

Please complete the following information:

Q1. Surname

Q2. Forename *(include up to two forenames)*

Q3. Date of birth (DD/MM/YYYY) / /

Q4. Gender *(Please tick appropriate box)*

Male	Female
☐	☐

Q5. Are you in the Army, RN/RM or RAF? *(Please tick appropriate box)*

Army	☐
RN/RM	☐
RAF	☐

Q6. Please tick the box appropriate to your rank.

Officer	☐
Other rank	☐

Q7. What is your service number?

Q8. What age were you (years old) when you joined the services?

Q9. Tick the box that is most appropriate to your cap badge, unit or branch.

Teeth arms/warfare (infantry/armour etc)	☐
Front line support (engineering, signals, artillery)	☐
Logistics/Supply/Other	☐

Q10. What is your current trade?

Q11. Were you posted overseas as part of any of the campaigns listed below:
(Please tick appropriate boxes)

	Yes	No
Gulf 1	☐	☐
Balkans	☐	☐
OpTELIC	☐	☐

Q12. Are you medically fit, i.e. P2, fit for full duties? *(Please tick appropriate box)*

Yes	No
☐	☐

ANNEX D: Executive Summary

Administrative Officer Briefing

1.1	**Project Title**	**DU Normative Value Study (Military)**
1.2	**Project Officer**	**Dr Andrew P Colvin, IOM**
1.3	**Associated Workers**	**Dr Colin Soutar, IOM** **Dr Brian Miller, IOM** **A Heather Tait, IOM** **Scott Dempsey, IOM** **Peter Hutchison, IOM**
1.4	**External Consultants**	**None**
1.5	**Independent Medical Officer**	**Wing Commander John Aitken**
1.6	**INM Task No.**	**RD033-01074**
1.7	**Customer Name**	**Ministry of Defence**
1.8	**Customer Code No.**	**RD033-01074**
1.9	**Tasking Reference**	**RD033-01074, 7/3/03**
1.10	**Establishments**	**Royal Navy, Army and RAF establishments**
1.11	**Location for Study**	**Tri-service bases as selected for inclusion**
1.12	**Experimental Dates**	**January to June 2004**

2 INTRODUCTION

IOM has been asked by Ministry of Defence (MoD) to design and undertake a cross-sectional survey of urine concentrations of depleted uranium in service personnel in the UK and Germany.

The MOD's Statement of Requirement is for the following:

- Design of a normative value study in conjunction with the MOD;
- Production of a protocol for the study;
- Obtaining ethical clearance for the study;
- The collection of the urine samples;
- The storage of the urine samples;
- Statistical analysis of the data and reporting;
- Publication of the work.

This research project has been prepared to meet these requirements, following discussions with MoD.

3 BACKGROUND

There have been concerns expressed by some, with considerable media attention, about the potential health effects of exposure to depleted uranium following active service in war zones where depleted uranium has been used. The Royal Society has acknowledged that there is a great deal of uncertainty in the assessment of DU exposure and has stressed the need to validate the measurement of urinary DU concentrations as a measure of past exposure. Since the publication of the Royal Society Report, the MOD's DU Oversight Board has overseen a programme of development work.

The use of DU is not confined to the military and some exposure to DU is likely to have occurred locally within the UK. For example, some contamination of the general environment is likely to have occurred around plants where nuclear fuel is processed or where DU is used in manufacturing.

Given the ongoing concern about the potential health effects of DU, the Ministry of Defence (MOD) has stated that biological monitoring for DU exposure will be available to any service personnel who have served in an area where DU has been, or may be, used. To support this commitment, MOD requires collection of a set of urine samples from service personnel (Navy, Army and Air Force) that can be used as a baseline for post-deployment testing, taking into account factors including occupation and location. The screening will include a urine test for uranium isotopes and total uranium.

The Institute of Occupational Medicine was invited to tender for this work, which is funded by the Ministry of Defence. The Project Officer and associated workers have no conflicts of interest to declare.

An additional summary of this project in lay language is given in the Subject Information Sheet at Annex A.

This research project has been submitted to MoD (Navy) Personnel Research and Ethics Committee for ethical approval, and has been scrutinised and approved with respect to ethical clearance.

4 AIM

The aim of this study is to characterise the overall distribution of values of urinary depleted uranium and uranium concentrations in military personnel in all three services.

5 METHODS

Units will be selected and all personnel available on the day of collection invited to volunteer to participate after an appropriate briefing. Random selection of personnel based on gender, rank and occupational group will then take place to determine study participants.

Study Subjects will be representative of gender, occupational groups and ranks within the service population as a whole. Written informed consent will be obtained from each subject and kept on file. The Subject Information Sheet is attached at Annex A and the Consent Form at Annex B. Also attached is the Subject Questionnaire at Annex C.

6 EXCLUSION CRITERIA

Personnel who had recently served in Iraq on Operation TELIC are excluded.

Reservists are excluded from the study since their lifestyle might not be representative of the British military population in general.

Only serving personnel stationed in the UK and western Europe will be sampled due to practical reasons.

IOM staff will elicit the above information by questionnaire at the time of urine collection and those who do not meet the criteria above will be excluded from the results. See Annex C for a copy of the initial questionnaire. In cases of doubt as to whether an exclusion criterion is present or not, subjects will be excluded.

7 PROCEDURES

7.1 Detailed description

7.1.1 Sample collection

IOM will arrange for the collection of urine samples and questionnaires from the specified number of individuals at locations agreed with the MOD during the study design process. It is assumed that MOD will provide nursing support for taking urine samples from female subjects. A short information sheet on the study that the local Administrative Officer will be able to use in their recruitment of volunteers is provided at Annex D.

An experienced member or members of IOM's medical team will supervise the collection of a minimum of 100 ml freshly voided urine samples from military personnel. Midstream specimens of urine or other special anti-contamination procedures are not considered necessary by IMN Analytical Laboratory staff. Nor is any immediate urine sample preparation required. Details of the IOM staff will be supplied to and approved by the MoD prior to the sample collection. The clinical supervision will include:

- briefing the study subjects on the purpose of the study, obtaining signed consent from the subject and administering the personal data questionnaire;
- information on the importance of adequate oral fluids before the collection starts.
- briefing the study subjects on how to give the sample, particularly with regard to avoiding sample contamination (MoD nursing assistance is requested for obtaining samples from female personnel).

The MOD have agreed to provide appropriate facilities (e.g. a medical room and nursing support) at each base for IOM's use on the days that sample collection is to be carried out. Local administrative support will be organised by the appointed location Administrative Officer.

Following collection, samples will be refrigerated. They will be transported back to either INM laboratory or IOM headquarters in Edinburgh at a temperature of 0° C to 4° C and transferred to a freezer as soon as is practicable after sample collection. Samples held at IOM headquarters will be stored no longer than five days before transfer to INM laboratory.

7.1.2 Staffing

This contract will be primarily undertaken within IOM's Medical Division and the Director of Medical Services, Dr Andrew Colvin, has overall responsibility for this work. Scott Dempsey, a senior occupational health technician and Heather Tait, a senior occupational health nurse are the staff most likely to be involved in the supervision of sample collection and the transport of samples back to Edinburgh (if required).

7.2 Withdrawal criteria

Subjects will stop on attaining the first of the following criteria:

(a) on the request of the subject;
(b) on the instruction of the Independent Medical Officer;
(c) on the decision of the Administrative Officer or IOM clinical staff;
(d) if the volunteer is unable to provide a urine sample within a practical timescale at the time of collection.

8 MEASUREMENTS

8.1 Personal data

Personal data needed for each individual by questionnaire includes:

- full name;
- gender;
- rank;
- date of birth;
- date, time and location of sample collection;
- age of joining services;
- branch/corps/unit or occupational group;
- any previous active service in the Balkans or in the Middle East;
- medical fitness category.

Laboratory analysis will be undertaken by INM for total urinary uranium contents and for the isotopic ratio of the uranium present. Results will be reported in terms of total uranium and DU concentrations in urine, scaled relative to creatinine. It is anticipated that the DU content of a substantial proportion of samples is likely to be at or below the limits of detection. The analysis is theoretically subject to interferences from mercury chloride or mercury argon compounds which have similar masses to U235 and U238, respectively. Some individuals may have relatively high levels of mercury in urine as a result of dietary exposure (fish) and exposure to mercury in dental amalgam. No analysis for mercury has been planned at this stage, but it may be considered later. The records received will be assumed to be complete and accurate.

8.1.1 Data protection and control

IOM will be Data Controller under the Data Protection Act, and has many years of experience in handling confidential research data. No individual study participants will be identified in the report.

8.2 Reporting

The report, in the form of an IOM Research Report, will include a brief executive summary, a scientific summary, introduction, methods, results and discussion. Personnel in the Institute of Naval Medicine will be invited to contribute to the authorship of the report. A draft will be submitted to MOD for comment before finalising. IOM will take these into account, but will retain final editorial control. To demonstrate openly the independence of the study, the contract will stipulate IOM freedom to publish. IOM Research Reports are publications with a small circulation, and are available on request. In addition, the work will be prepared for submission in due course to a peer-review scientific journal.

A copy of the principal reports(s) covering this work will be submitted to the Secretary of MoD(N) PREC on publication.

It is not planned to routinely release individual results, but it is a requirement under the Data Protection Act to release individual information if requested in writing by individual study subjects and the true cost of providing the information by IOM is met prior to disclosure.

9 MEDICAL AND ETHICAL CONSIDERATIONS

IOM has obtained ethical clearance for the study by submitting a study protocol to the MoD (Navy) Personnel Research Ethics Committee, for scrutiny and ethical approval. The study will observe and comply with all the limitations defined in the Schedule of Approved Procedures as issued by the Ministry of Defence (Navy) Personnel Research Ethics Committee.

Each volunteer will be invited to sign a consent form having been given adequate time to consider their decision to volunteer. Individuals will be provided with information by a printed information sheet and given the opportunity to ask questions of a member of the study team (either in person or by telephone). A copy of the subject information sheet and consent form will be included with the protocol submitted for ethical approval.

9.1 Medical cover

IOM staff will supervise the collection and transport of urine samples. The project leader, Dr AP Colvin will be on call by telephone as a source of advice or guidance to volunteer subjects, IOM clinical staff and to the local Administrative Officers during the study. Wing Commander John Aitken will be on call for advice and guidance to Administrative Officers if required by telephone during the study collection phase.

9.2 Compliance

This study complies, and at all times will comply, with the Declaration of Helsinki, as adopted at the 52nd WMA General Assembly, Edinburgh, October 2000, and with the Draft Additional Protocol to the Council of Europe Convention on Human Rights and Biomedicine on Biomedical Research (CGBI/INF (2001) 5 dated 18 July 2001).

9.3 Compensation

All subjects will enjoy the benefits provided by the MoD extant no-fault compensation scheme, and will be fully informed of that scheme and provided with written details.

10. HAZARDS TO SUBJECT SAFETY

10.1 Pregnancy and lactation

No measures to exclude potentially pregnant women are anticipated as being required.

11 SUBJECT PAYMENTS

In view of the innocuous nature of the trial, no subject payments are proposed.

APPENDIX 2: SITE LIAISON DOCUMENTS

IOM Survey Co-ordinator : Local Liaison Officer –

Liaison information sheets

IOM Co-ordinator

Peter Hutchison will be the IOM's principal contact for each site's Local Liaison Officer (LLO) or their deputies.

IOM will ensure that LLO's have received the following paper work:-

- Contact details of IOM staff undertaking the study – essentially a list of the IOM's project team.
- DU Normative Study Protocol.
- IOM Subject Information Sheet (Annex A of Study Protocol)
- Check list of issues that will need to be covered prior to field work commencing.

The LLO will be contacted by IOM following receipt of paperwork to discuss details/problems/issues.

Dr Brian Miller of IOM will contact separately to discuss sample selection criteria for each site.

Local Liaison Officer responsibilities

- Provide contact details of key staff at the site.

- Domestic arrangements for IOM clinical staff
  i.e. Where and to whom do they report on arrival at base;
  availability of overnight accommodation;
  inform IOM of any local regulations;
  mess arrangements.

- Instruct IOM survey staff about health and safety procedures for the areas they will be working in (fire drill, emergency contact numbers etc).

- Arrange security passes (if required) for IOM survey staff.

- Provide IOM with site map and travel directions

- Peter Hutchison will liaise with INM (Institute of Naval Medicine) to arrange delivery of sample transport cases c/w bottles and locks. These will (usually) be delivered directly to the survey site and it will be the responsibility of the LLO to arrange for these to be securely stored pending the arrival of IOM survey staff.

- Agree with IOM, a method of informing subjects about the study prior to subject selection

- Provision of clerical/nursing assistant to support IOM staff to conduct survey – this may include some assistance with questionnaire administration and collection of completed forms.

- Working hours will be agreed with IOM prior to survey dates (see below for further details of working hours).

- Co-ordination of appointment system, this will include transport of individuals to the area, it is estimated that each appointment will take approximately 10 minutes although 10 subjects per hour is probably workable. An outline of the programme of work will have been confirmed with IOM staff before the appointments are made.

- Practical details about the appointment system and transport arrangements need to be sent to IOM survey co-ordinator and IOM survey staff.

- Subject selection will be in compliance with the sampling protocol agreed after discussions with Dr Brian Miller (IOM).

- If practicable, a full appointment list should be emailed to Peter Hutchison prior to the dates of the survey. The same list should be made available to IOM survey staff on their arrival to the site.
- LLO will inform all subjects about appointment times and transport arrangements.

- Ensure all volunteers have been provided with and read **IOM Subject Information Sheet** (Annex A of the Study Protocol). Ideally, this information sheet should be issued to volunteers 1-2 days before their appointment

- Individuals should attend on time for their appointment (if required, they will be asked to present ID to IOM survey staff).

- LLO may be requested to arrange for the dispatch (by IOM appointed courier) of samples in locked cases to INM (Institute of Naval Medicine).

The IOM survey co-ordinator and IOM survey staff must be kept informed about any changes that may be required to the agreed procedures. In turn, IOM survey co-ordinator will keep LLO's and their staff aware of any changes that IOM staff may need to make to agreed procedures.

Subject Requirements

- Each subject will give informed consent by completing and signing a consent form prior to any data collection or any request for providing a urine sample.

- Each subject will complete a short questionnaire, assisted by a member of the IOM team/administrative staff.

- Subjects will be given instruction by IOM staff on the provision of a urine specimen and will be requested to then provide a sample of urine.

- Subjects are requested to remove any bulky outer garments, such as coats. If practicable this should be done before arrival at the study centre.

IOM staff - Hours of Work

IOM survey staff will be prepared to work flexible working hours; an 8 hour day can be encompassed between the hours of 7.30 am and 7pm. A half hour break will be required for lunch. Weekend or evening work may also be possible but will require confirmation of availability of staff.

List of facilities/requirements for study centre

It is recognised that not all the requirements will be able to be met at all sites – the list is for guidance and requirements will be discussed as part of contact between IOM's survey co-ordinator and each sites LLO.

- Survey facilities to be located in a suitable location to take account of requirements of the survey and the transportation of subjects to and from the unit.
- Waiting/reception area – preferably with seats and tables
- A clean, warm room which can maintain privacy and thereby ensure confidentiality and security.
- A lockable facility for the secure storage of samples and completed forms.
- A minimum of one table and two chairs in the room.
- Yellow bags for the disposal of clinical waste.
- Wash hand basin, towels
- Power source
- Toilets minimum of two:- male/female
- Drinking water / cups

Details of IOM staff contact

Removed from final report

Institute of Occupational Medicine

WORLD HEALTH ORGANISATION
COLLABORATING CENTRE
FOR OCCUPATIONAL HEALTH

Applying science for a better working environment

The Institute of Occupational Medicine

The IOM is a major independent centre of scientific excellence in the fields of occupational and environmental health, hygiene and safety. We aim to provide quality research, consultancy and training to help to ensure that people's health is not damaged by conditions at work or in the environment. Our principal research disciplines are exposure assessment, epidemiology, toxicology, ergonomics and behavioural and social sciences, with a strong focus on multi-disciplinary approaches to problem solving.

Our beginnings

Our first major research programme began in the 1950s, on respiratory health problems in the coal mining industry. Major themes were quantification of airborne dust concentrations in different jobs, characterisation of types and constituents of the dusts, measurement of health effects, relationships between exposure and disease, and proposals for prevention. This research became an international benchmark for epidemiological studies of occupational health, and was the primary influence on dust standards in mines in the UK, US and other countries.

Current themes

Our current work spans many other industries including asbestos, MMMF, pesticides, chemicals, energy, telecoms, metals, textiles, construction, agriculture as well as the environment. While diseases of the respiratory tract remain a major interest, our scope now extends to many other health outcomes such as mortality, cardiovascular effects, cancer, back pain, upper-limb disorders, hearing loss, skin diseases, thermal stress and psychological stress. Related work includes the development and application of measurement and control systems, mathematical models and survey methods.

Who we work for

Our work in these areas is conducted for a wide range of organisations in the UK, the EU, and the US, including Government departments, international agencies, industry associations, local authorities, charitable organisations, and industrial and commercial companies. The IOM is a World Heath Organisation (WHO) collaborating centre and is an approved institute of the Universities of Edinburgh and Aberdeen, enjoying collaborative research links with NIOSH, IARC, and many other institutes throughout the world.

Publication

We believe that our research findings should be publicly available and subject to the scrutiny of the international scientific community. We publish our findings in the peer reviewed scientific literature and through our own series of Research Reports.

Contact

For further information about the IOM's research capabilities:

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