MINISTRY OF DEFENCE
Main Building, Whitehall, London, SW1A 2HB
Telephone (Direct Dialling) 020-7807-8774
(Switchboard) 020-7218-9000
Facsimile 020-7807-8834

From Brigadier L P Lillywhite MBE MSc MB BCh MFOM
Director of Medical Personnel, Training and Policy
Surgeon General's Department

D/SG(Med Pol)/350/6/7

See Distribution 13 February 2001

THE PROPOSED INTRODUCTION OF A VOLUNTARY SCREENING PROGRAMME FOLLOWING HEALTH CONCERNS IN RESPECT OF DEPLETED URANIUM

1. On 9th January, in response to the health concerns of veterans arising from allegations in respect of Depleted Uranium (DU), the Minister for the Armed Forces announced that MOD would identify an "additional appropriate voluntary screening programme for our service personnel and civilians who have served in the Balkans. We will do this on the basis of the best available science. We will consult appropriate national bodies including the UK national screening committee of the UK Departments of Health". He stated that MOD would take into account the report currently under preparation by the Royal Society that is taking an independent look at DU, and that UK would also seek to co-ordinate its approach with allies, many of whom are addressing the same issues. It is MOD's intention that the screening initiative should be equally applicable to Gulf veterans

2. The Surgeon General set up an Expert Advisory Group (EAG) to address the medical and technical issues of introducing such a programme. The report of the EAG is attached, together with a commentary and questions that MOD believes is raised by the report.

3. The Surgeon General invites comments on the issues. In order to enable MOD to consult on draft screening proposals in March, any comments are requested by 9th March 2001, either by post or alternatively by email to dmedperspol@lillywhi.demon.co.uk.

L P LILLYWHITE
Brigadier
for Surgeon General

Encl.

1. Consultation Document

Distribution:

External to MOD:

Royal Society
Royal College of Physicians, Faculty of Occupational Medicine

Royal College of Physicians, Faculty of Public Health Medicine (PS to President)
Royal College of General Practitioners
Society of Occupational Medicine
Cabinet Office, Office of Science and Technology
Government Chief Scientific Adviser
CMO Department of Health
CMO Wales
CMO Scotland
CMO Northern Ireland (and Chair UK National Screening Committee)
HSE
Medical Advisory Committee of British Members Council of the World Veterans Federation (c/o The Royal British Legion)
CMO British Red Cross
Dr Muir Gray (Programme Director, UK National Screening Committee)
Committee of Medical Aspects of Radiation in the Environment (COMARE)
NRPB
COMARE
NATO, Partnership for Peace and Troop Contributing Nations (via Ad Hoc Committee) (via Balkans Secretariat 1a)
University of Sheffield
University of Manchester
Royal Holloway College
Sure Screen Diagnostics
Portsdown West
Marsh Medical
Harwell Scientifics
US National Institute of Standards and Technology

Internal:

Medical Director General Navy
Director General Army Medical Services
Director General Medical Services (RAF)
Defence Evaluation and Research Agency
Chairman Defence Scientific Advisory Committee
Chief Scientific Adviser MOD
Defence Radiological Protection Service
Director of corporate Research, Ministry of Defence (DR(C))
Gulf Veterans' Illnesses Unit
Head of Gulf Veterans' Medical Assessment Programme

Ministry of Defence

Introduction of a Voluntary Screening Programme Following Health Concerns in Respect of Depleted Uranium

An invitation to professional and official bodies to comment on technical issues

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12 February 2001

THE INTRODUCTION OF AN APPROPRIATE VOLUNTARY SCREENING PROGRAMME AS A RESULT OF CONCERNS ON DEPLETED URANIUM

An invitation to professional and official bodies to comment on technical issues

BACKGROUND

1. On 9th January, in response to the health concerns of veterans arising from allegations in respect of Depleted Uranium (DU), the Minister for the Armed Forces announced that MOD would identify an "additional appropriate voluntary screening programme for our service personnel and civilians who have served in the Balkans. We will do this on the basis of the best available science. We will consult appropriate national bodies including the UK national screening committee of the UK Departments of Health". He stated that MOD would take into account the report currently under preparation by the Royal Society that is taking an independent look at DU, and that UK would also seek to co-ordinate its approach with allies, many of whom are addressing the same issues.

2. On 15th January, there was a meeting of the heads of NATO's military medical services (COMEDS)[1] to consider the weight of evidence for specific health risks to those who were serving, or had served, in the Balkans, including risks from Depleted Uranium. COMEDS recognised that there are legitimate health concerns that need addressing, but also noted that similar concerns arose after all conflicts and that in the Balkans DU was but one of many potential hazards to health. COMEDS agreed a series of measures for the NATO nations to take forward. NATO's Military Committee has subsequently agreed these[2].

3.1 In order to substantiate any valuable medical conclusion, the following approaches/measures have been agreed upon:

3.1.1 Each nation should analyze its military personnel crude mortality rates, and age-specific mortality rates (ASR). These rates should be calculated separately for the deployed and for non-Balkan deployed military personnel and should be compared. A comparison with the general population should also be made. Each nation should analyze the overall and/or specific rate of malignancies occurrence within its Balkan veterans, and compare it to their national matched statistics.

3.1.2 Each nation should correlate the collection of morbidity data with known local health hazards in theater.

3.1.3 The coordinated implementation of 3.4 will be performed by the COMEDS through its WG on Military Preventive Medicine that will report to the next plenary meeting (May 2001).

3.1.4 COMEDS insists that any investigation and measurements ought only to be undertaken where they are scientifically-validated and ethically acceptable.

Box 1: COMEDS Recommendations

3. The COMEDS strategy can be summarised as the use of epidemiology to identify and characterise any ill health arising from service in the Balkans; implementation in the Balkans of measures to identify and minimise risks to health; and the introduction of investigations and tests only where these meet scientific and ethical criteria.

4. The UK supports the COMEDS strategy. It is discussing with the MRC the structure of an appropriate epidemiological study into the health of those who have served in the Balkans; the structure of such a study or studies will not be discussed further in this consultation document. The UK is also considering what further research is specifically required into DU, and will be consulting on such a programme separately. Except where research is required to

[1] COMEDS – Committee of the Chiefs of Military Medical Services in NATO.
[2] MCM-013-01 dated Jan 01

support a screening programme, research is therefore not further considered in this consultation document.

SCOPE

5. The balance of this consultation document addresses the "additional appropriate voluntary screening programme" announced by Ministers. It is primarily concerned with the scientific and medical issues of screening for exposure to DU. It does not address in detail at this stage what screening should be given to specific groups (eg Gulf or Balkans Veterans). This will be addressed once the scientific and medical issues have been resolved.

TIMETABLE

6. Following the statement by the Minister on 9th January, MOD set up an Expert Advisory Group (EAG), under the leadership of the Medical Officer in Charge of the Institute of Naval Medicine, to address technical issues related to screening. They were required to report to MOD by 31st January.

7. This consultation document seeks views on a number of issues arising from the report of the EAG (including its Terms of Reference) which is attached as an enclosure. The consultation period ends on 9th March.

8. MOD then intends to bring forward by 24th March proposals for an appropriate voluntary screening programme, taking into account any responses to this document, and to consult on them with both the scientific and medical community and with Veterans groups and bodies representing veterans.

9. However, we will also take account of the eventual report of the Royal Society, and will co-ordinate our work with those of our allies (which now include NATO nations, Partnership for Peace nations and other troop contributing nations with personnel deployed now, or in the past, in the Balkans). This commitment may require the timetable to be modified.

SCREENING

10. The word screening has no universally accepted definition. Even within medicine, it refers to more than one type of action or activity. When discussing screening it is therefore necessary to define in each circumstance what is meant. For the purpose of this consultation document we have based our definitions of occupational and population screening on those used by the EAG, and summarised In Box 2. The EAG did not consider Health Screening, although it is included within this consultation document.

Occupational Screening: The use of a test or tests on individuals in order to confirm the effectiveness of control measures or to control an individual's exposure to a health hazard.

Population Screening: The use of a test or tests on individuals who may have been exposed at some time in the past, and where there is concern that the exposure might adversely affect physical or psychological health**.**

Health Screening: The provision of a clinical assessment, supported by appropriate tests, to confirm (in so far as possible) the absence of disease in a healthy but concerned person, or consider causative factors in an ill person.

Box 2: Definition of Screening

11. When considering screening, MOD is bound to take account of the views of those authorities and bodies set up by Government to advise it on matters concerning such screening. The Health and Safety Executive advises or requires occupational screening to be used in specific circumstances. The National Screening Committee has been set up by the UK Departments of Health to advise Government on population screening issues. There are also other independent bodies set up by Government to advise them on specific issues, such as COMARE, whose views MOD must take into account. MOD will also take

account of the views of other professional bodies who have a particular interest in the matters being debated, such as the Royal Society and medical Royal Colleges. A list of those to whom this consultation document has been sent is at Annex A. A number of Universities and other individuals and institutions have also offered suggestions and advice; where these are novel and not yet incorporated into normal clinical or health and safety practice, MOD will only consider them if such proposals are supported by appropriate external bodies. A list of such submissions is at Annex B

CHOICE OF SCREENING TESTS

12. The EAG addresses the choice of screening tests in general in section 5 and in more detail in Annex C of its report. Comments are invited on the following

a. Question 1: To what extent should MOD rely on current ICRP recommendations and advice?

b. Question 2: Does whole body monitoring have a part to play in screening?

c. Question 3: Does analysis of bone using *K x-ray fluorescence*, or analysis of hair, blood, faeces or tooth enamel for uranium have any part to play in any screening programme to be established in 2001?

d. Question 4: For exposures occurring some time in the past, the EAG conclude that DU must be sought directly (rather than first testing for total uranium). They further conclude that Thermal Ionisation Mass Spectrometry (TIMS) is the only test capable of detecting exposures more than 2 years previously, and then only if the exposure was significantly high. By implication they conclude that TIMS is the only suitable test for population screening. However, the EAG states that a technique for use on biological samples has yet to be validated and there are no laboratories accredited to undertake such work. Are these conclusions valid and if so what are the implications for a screening programme?

e. Question 5: For relatively high concentrations of DU in the urine (eg from a recent occupational exposure or from retained foreign bodies containing DU) the EAG states that High Resolution Inductively Coupled Plasma Mass Spectrometry is a validated test. However, its validity depends on the excretion in urine of DU being 1½ times the natural background uranium concentration. It would thus seem a valid test only for recent or current exposures. Is this a valid conclusion?

f. Question 6: The EAG state that Inductively Coupled Mass Spectrometry is a validated test for total urinary uranium, but the normal values in the population are not accurately known, nor is it known whether the values in those deploying on operations conform to the normal population values. The test does not differentiate between natural uranium and DU. Is it correct to conclude that it is not appropriate for screening personnel for past exposure (except perhaps for those with retained foreign bodies that might include DU), but it could quickly be developed as a measure of current exposure?

OCCUPATIONAL SCREENING

13. Occupational screening is addressed by the EAG at Section 8 of its report. Occupational screening is but one part of any strategy to minimise the risk from a particular hazard. It is recognised that DU is a potential hazard that in certain circumstances can pose a risk to health. The normal health and safety approach to any hazard is to first seek to eliminate it by finding a suitable alternative, and if this is not feasible to prevent exposure, and where exposure is not preventable, to control that exposure. Research is being undertaken to find an effective replacement for DU, but until such time as a replacement is found DU will be used on battlefields. Isolating areas where DU rounds have struck can prevent exposure. Where

exposure cannot be prevented, it can be limited by minimising the time exposed (eg to rescue injured personnel inside struck vehicles) or by wearing protective clothing.

14. Any occupational screening must thus form part of a wider health and safety strategy. There is no reason why in a Theatre of military operations where there is no significant enemy activity, the normal peacetime approach to health and safety should not be adopted by military forces. The same is not the case during active military operations where there is an enemy seeking to kill ones own troops. In such circumstances, any precautions taken to minimise the risk from a hazard must necessarily take account of the extent to which military operations are degraded by the proposed precautions and the consequent risk of death from enemy action and other hazards increased. For example, for practical logistic reasons, only a limited number of environmental health personnel can be deployed on an active battlefield and during active operations their highest priority task is the prevention of acute illness from water, food, or insect borne diseases. During such periods monitoring for hazards such as DU takes second place. Similarly, in order to rescue an injured crewmen in an armoured vehicle hit by DU, the balance of risk (a potential, unproven, future risk of illness versus an otherwise imminent death) would favour rescuers entering the vehicle for a short time with only minimal precautions. Nevertheless, even on a battlefield, personnel in a field workshop who had to spend a significant time in a damaged vehicle hit by DU should take appropriate precautions.

15. However, the duty of care owed to Servicemen requires that as far as practical exposure is limited, and that if exposure to a hazard occurs, it is measured as soon as possible both in the environment and (where appropriate and feasible) in the body. As well as contributing to a comprehensive health and safety strategy, such measurement will also facilitate investigation of any future ill health in either individuals or in the military population (including veterans). In respect of DU, it seems reasonable that biological monitoring should play a part.

16. In respect of occupational screening:

a. Question 7: MOD believes a coherent policy that includes biological monitoring should be developed for measuring and controlling exposure on future battlefields. Is it reasonable to rely on Inductively Coupled Mass Spectrometry for total urinary uranium, backed up in the case of a positive result by High Resolution Inductively Coupled Plasma Mass Spectrometry? What value for total urinary uranium should constitute a positive?

b. Question 8: The EAG raise a number of issues that question the utility of the measurement of total urinary uranium for those currently in the Balkans, or recently returned from it. Nevertheless, should a programme be initiated of voluntary anonymous testing of an appropriate cohort of Balkans personnel both as part of research to ascertaining the normal values and to confirm that significant exposures are not occurring?

c. Question 9: To what extent should occupational screening be targeted and, once normal population values are known, is there a need for a baseline, pre-deployment, measure as suggested by the EAG?

d. Question 10: In the context of occupational screening, should screening be voluntary or should it be treated on the same lines as occupational lead or radiation screening?

17. Clearly, any screening programme must take into account the question of what to do in the event of positive results; this is addressed later.

POPULATION SCREENING

18. Population screening poses the most difficult questions. Those who would like such tests appear to be those who may have been exposed some significant time ago and the Minister clearly included these in his announcement on screening. The EAG's discusses

population screening, its aims and objectives, possible tests and the questions they might answer, and an outline methodology. However, as its discussion on testing indicates, there is no currently validated test sensitive enough to identify past exposures and such a programme is dependent on a significant amount of prior development work. It is also unlikely that any proposals for population screening would meet all of the criteria of the UK Departments of Health National Screening Committee (although it is not necessary for a population screening test to meet all the criteria). An extract from the National Screening Committees Second Report[3], showing the criteria, is enclosed for reference at Annex C.

19. An alternative to population screening for DU might be a research programme to seek to identify DU in personnel known to have been exposed, both on and off the battlefield. Such research would help determine the need and utility of a population screening programme and might also fulfil some of the functions of the pilot study recommended by the EAG.

20. Another alternative to screening for DU would be to screen for any specific disease caused by uranium. However, there is currently no specific disease that can be causally attributed to uranium exposure on the battlefield, and the EAG do not believe that any screening test based on disease outcome is appropriate. Clearly, this conclusion might need revisiting in the light of the results of any epidemiological studies referred to in Paragraph 4.

21. Answers are sought to the following questions:

a. Question 11: Is it accepted that population screening could only be introduced after the further work recommended by the EAG?

b. Question 12: Is it accepted that screening based on a specific disease is inappropriate?

c. Question 13: Would the more limited testing, outlined in Paragraph 19. be appropriate?

MANAGEMENT OF POSITIVE RESULTS

22. It would be unethical to introduce screening without deciding in advance what action to take in the event of positive results, however remote the likelihood of such a result. For occupational screening there are clear benefits, as positive results would lead to enhanced control measures (so reducing future exposures to all) and an individual with a positive result would be either prevented from having further exposure, or his future exposure would be controlled via individual monitoring. Current occupational testing for lead or radiation exposure provide clear precedents for such occupational screening.

23. What to do in the event of a positive result from population screening would be much more problematical. There is no “treatment” for residual DU, and there is no disease that DU is known to cause that can be sought in those who are positive. It would satisfy those who are curious, but possibly at the price of psychological ill health. Some may wish confirmation of past exposure to support legal action, but whilst it might be reasonable for individuals to seek such evidence on an individual basis such a motive should not justify population screening.

24. Two questions arise:

a. Question 14: Is it correct to conclude that no action can be taken in the event of a positive result during population screening, other than seeking to provide reassurance?

b. Question 15: Assuming population screening is technically feasible, is it acceptable to risk identifying positives, for whom there is no treatment, in order to give reassurance to those who will test negative?

[3] Second Report of the National Screening Committee, Annex C http://www.doh.gov.uk/nsc/pdfs/secondreport.pdf

HEALTH SCREENING

25. The EAG did not address health screening (which they referred to as health assessment). Nevertheless, MOD considers that a clinical facility (which for the purpose of this consultative document, we term a Veterans Assessment Centre (VAC)) where Servicemen and Veterans can be examined and investigated has merit. The clinicians in the VAC would be knowledgeable on the issues, such as DU, PTSD, and organophosphates that feature from time to time amongst veterans health concerns. The VAC would inform, counsel, examine and, if indicated, investigate an individual's health state. For those with established disease, further investigations would if necessary be undertaken to establish whether there might be a causative relationship to an occupational exposure occurring during service. The existing Gulf Veterans Medical Assessment Programme provides a partial model.

26. Question 16: Does a Veterans Assessment Centre have a part to play in addition to, or in place of, a population screening programme?

27. Question 17: Are there any particular models or types of location for the establishment of a Veterans Assessment Centre which would best meet the health screening needs of veterans?

OTHER ISSUES AND QUESTIONS

28. Question 18: Are there any comments on the EAG's paragraphs on other core technical issues?

29. Question 19: Are there any comments on the EAG's discussion on important analytical issues?

30. Question 20: Are any of the proposals received by MOD and listed at Annex B of practical relevance to the introduction of occupational and population screening.

31. Question 21: Are there any issues that are not exposed in this consultative document, and is there a completely different approach that could be taken by MOD?

LIST OF QUESTIONS

32. A consolidated list of Questions is at Annex D. These are provided to assist those who intend responding, but it is not expected that all those consulted will wish to respond to all questions, and many might wish to make a more general response.

33. Replies are sought by 12 March, by post or (preferably) via email to dmedperspol@lillywhi.demon.co.uk . Queries should be addressed to Brigadier Louis Lillywhite, Director of Medical Personnel, Training and Clinical Policy by email or on (020) 7807 8774

Annexes:

A. List of those initially consulted.
B. List of Submissions Received by Ministry of Defence.
C. National Screening Committee Criteria for a Screening Test.
D. Consolidated List of Questions.

LIST OF THOSE INITIALLY CONSULTED

External to MOD:

Royal Society
robert.may@royalsoc.ac.uk
Royal College of Physicians, Faculty of Occupational Medicine
president@facoccmed.ac.uk
Royal College of Physicians, Faculty of Public Health Medicine (PS to President)
louiseallcoat@fphm.org.uk
Royal College of General Practitioners
president@rcgp.org.uk
Society of Occupational Medicine
nicholson.pj@pg.com
Cabinet Office, Office of Science and Technology
No email address available
Government Chief Scientific Adviser
csa@csa.mod.uk
Department of Health
dhmail@doh.gov.uk
CMO Wales
ruth.hall@wales.gov.uk
CMO Scotland
cmo@scotland.gsi.gov.uk
CMO Northern Ireland (and Chair UK National Screening Committee)
henrietta.campbell@dhsspsni.gov.uk
HSE
timothy.walker@hse.gsi.gov.uk
Medical Advisory Committee of British Members Council of the World Veterans Federation (c/o The Royal British Legion)
jpowell@britishlegion.org.uk
CMO British Red Cross
jpaterson@redcross.org.uk
Dr Muir Gray (Programme Director, UK National Screening Committee)
muir.gray@his.ox.ac
Committee of Medical Aspects of Radiation in the Environment (COMARE)
NRPB
nrpb@nrpb.org.uk
COMARE
B.A.Bridges@sussex.ac.uk
NATO, Partnership for Peace and Troop Contributing Nations (via Ad Hoc Committee)
Those listed in Annex B

Internal:

Medical Director General Navy
Director General Army Medical Services
Director General Medical Services (RAF)
Defence Evaluation and Research Agency
Chairman Defence Scientific Advisory Committee
Chief Scientific Adviser MOD
Defence Radiological Protection Service
Director of corporate Research, Ministry of Defence (DR(C))
Gulf Veterans Illnesses Unit

Annex B to D/SG(Med Pol)
Dated 3 Feb 2001

LIST OF SUBMISSIONS RECEIVED BY THE MINISTRY OF DEFENCE

Test proposed	Researcher	Centre	Notes
High Resolution Inductively Coupled Plasma Mass Spectrometry (ICPMS)	Prof. McLeod Dr C Pickford chris.pickford@harwell.scientifics.com	University of Sheffield Harwell Scientifics	Limit of DU detection in urine when DU concentration was about 1.5 times that of background natural uranium
Leukaemia Screen	Dr G M Taylor	University of Manchester	Research experimental test to detect leukaemia. Initial results to be presented to British Society for Haematology in April 01.
Electron paramagnetic Resonance Dosimetry of Dental Enamel	(letter to eBMJ) R Mould	US National Institute of Standards and Technology	Reported as being able to estimate doses down to 20 millisieverts
DR 70 Cancer Screen	JG Campbell	Sure Screen Diagnostics	Screen for various types of cancer
Uranium Isotope analysis	Prof. Thirlwell	Royal Holloway College	
LIB Spectroscopy	Dr N Wood	Portsdown West	
Screening for Kidney Disease		Marsh Medical	

NATIONAL SCREENING COMMITTEE CRITERIA FOR APPRAISING THE VIABILITY, EFFECTIVENESS AND APPROPRIATENESS OF A SCREENING PROGRAMME [1]

The criteria, which are set out below, are based on the classic criteria first promulgated in a WHO Report in 1966 but take into account both the more rigorous standards of evidence required to improve effectiveness and the greater concern about the adverse effects of healthcare. Regrettably some people who undergo screening will suffer adverse effects without receiving benefit from the programme.

These criteria have been prepared taking into account international work on the appraisal of screening programmes, particularly that in Canada (2) and the United States (3). It is recognised that not all of the Criteria and questions raised in the Format will be applicable to every proposed programme, but as many as possible should be answered since this will assist the NSC to make quicker and better evidence based decisions.

All of the following criteria should be met before screening for a condition is initiated:

The condition
1.1. The condition should be an important health problem.
1.2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, or disease marker and a latent period or early symptomatic stage.
1.3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.

The test
1.4. There should be a simple, safe, precise and validated screening test.
1.5. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
1.6. The test should be acceptable to the population.
1.7. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

The treatment
1.8. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
1.9. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
1.10. Clinical management of the condition and patient outcomes should be optimised by all health care providers prior to participation in a screening programme.

The screening programme
1.11. There must be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (e.g. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

[1] Extracted from National Screening Committee Web Site at http://www.doh.gov.uk/nsc/library/lib_ind.htm

1.12. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.
1.13. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
1.14. The opportunity cost of the screening programme (including testing, diagnosis, treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).
1.15. There must be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.
1.16. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be made available prior to the commencement of the screening programme.
1.17. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.
1.18. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.
1.19. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

References:
Department of Health. *Screening of pregnant women for hepatitis B and immunisation of babies at risk.* London: Department of Health, 1998. (Health Service Circular: HSC 1998/127)
Wilson JMG, Jungner G. Principles and practice of screening for disease. Public Health Paper Number 34. Geneva: WHO, 1968.
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Holland WW, Stewart S. Screening in Healthcare. The Nuffield Provincial Hospitals Trust, 1990.
Gray JAM. Dimensions and definitions of screening. Milton Keynes: NHS Executive Anglia and Oxford, Research and Development Directorate, 1996.

Annex D to D/SG(Pol) 350/6/7
Dated 3 Feb 2001

CONSOLIDATED LIST OF QUESTIONS

Question 1: To what extent should MOD rely on current ICRP recommendations and advice?

Question 2: Does whole body monitoring have a part to play in screening?

Question 3: Does analysis of bone using *K x-ray fluorescence*, or analysis of hair, blood, faeces or tooth enamel for uranium have any part to play in any screening programme to be established in 2001?

Question 4: For exposures occurring some time in the past, the EAG conclude that DU must be sought directly (rather than first testing for total uranium). They further conclude that Thermal Ionisation Mass Spectrometry (TIMS) is the only test capable of detecting exposures more than 2 years previously, and then only if the exposure was significantly high. By implication they conclude that TIMS is the only suitable test for population screening. However, the EAG states that a technique for use on biological samples has yet to be validated and there are no laboratories accredited to undertake such work. Are these conclusions valid and if so what are the implications for a screening programme?

Question 5: For relatively high concentrations of DU in the urine (eg from a recent occupational exposure or from retained foreign bodies containing DU) the EAG states that High Resolution Inductively Coupled Plasma Mass Spectrometry is a validated test. However, its validity depends on the excretion in urine of DU being 1½ background uranium concentration. It would thus seem a valid test only for recent or current exposures. Is this a valid conclusion?

Question 6: The EAG state that Inductively Coupled Mass Spectrometry is a validated test for total urinary uranium, but the normal values in the population are not accurately known, nor whether the values in those deploying on operations conform to the normal population values. The test does not differentiate between natural uranium and DU. Is it correct to conclude that it is not appropriate for screening personnel for past exposure (except perhaps for those with retained foreign bodies that might include DU), but it could quickly be developed as a measure of current exposure?

Question 7: MOD believes a coherent policy should be developed for measuring and controlling exposure on future battlefields that includes biological monitoring. Is it reasonable to rely on Inductively Coupled Mass Spectrometry for total urinary uranium, backed up in the case of a positive result by High Resolution Inductively Coupled Plasma Mass Spectrometry? What value for total urinary uranium should constitute a positive?

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Question 9: To what extent should occupational screening be targeted and, once normal population values are known, is there a need for a baseline, pre-deployment, measure as suggested by the EAG?

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Question 11: Is it accepted that population screening could only be introduced after the further work recommended by the EAG?

Question 12: Is it accepted that screening based on a specific disease is inappropriate?

Question 13: Would the more limited testing, outlined in Paragraph 19. be appropriate?

Question 14. Is it correct to conclude that no action can be taken in the event of a positive result during population screening, other than providing reassurance?

Question 15. Assuming population screening is technically feasible, is it acceptable to risk identifying positives, for whom there is no treatment, in order to give reassurance to those who will test negative?

Question 16: Does a Veterans Assessment Centre have a part to play in addition to, or in place of, a population screening programme?

Question 17: Should referral be only via an individual's GP or consultant or should an individual be able to self refer?

Question 18: Are there any comments on the EAG's paragraphs on other core technical issues?

Question 19: Are there any comments on the EAG's discussion on important analytical issues?

Question 20: Are any of the proposals received by MOD and listed at Annex B of practical relevance to the introduction of occupational and population screening.

Question 21: Are there any issues that are not exposed in this consultative document, and is there a completely different approach that could be taken by MOD?

INM 252/122/1 31 Jan 2001

THE INTRODUCTION OF SCREENING IN RESPONSE TO CONCERNS THAT DEPLETED URANIUM CAUSES ILL HEALTH:
Report by Surgeon General's Expert Advisory Group on Screening for DU

INTRODUCTION

1.1 Over recent months the British government (and other NATO nations) have come under intense pressure to introduce screening tests for Service personnel and civilians who may have been exposed to Depleted Uranium (DU) during their deployment to the Balkans or the Gulf. The Government recognises the need to provide reassurance but is also mindful of the need not to raise unjustifiable concerns by the application of invalid tests. Consequently, the Minister for the Armed Forces has announced that a voluntary screening programme is to be identified. It is the intention that where appropriate this programme will be offered to all Service personnel and civilians who have participated on operational deployments in the Balkans or the Gulf and who are concerned that they may have been in contact with DU.

1.2 Furthermore, the Minister also announced that for people serving in the Balkans at present, and in the future, the existing environmental surveillance would be enhanced; this enhancement will include a DU screening programme.

1.3 The Surgeon General's Department has appointed an Expert Advisory Group to address the technical aspects of screening for DU and consider the suitability and availability of different screening tests. The recommendations of the advisory group are to be based on the best scientific information available and will be subject to independent scrutiny (Terms of Reference at Annex A).

1.4 The UK National Screening Committee (NSC) has been consulted to determine if a Population Screening Programme can meet the NSC criteria for screening. The NSC exists to help develop, introduce and audit appropriate screening programmes and it is prepared to form a view on MoD proposals and give advice accordingly. During the consultation process Dr J A Muir Gray CBE, the NSC Programme Director, provided invaluable advice on a range of issues relevant to the proposed Population Screening Programme.

1.5 The initial findings of the advisory group are presented. Technical issues, such as the choice of suitable screening tests, are described and the limitations of available tests explained (including UK capacity to undertake such tests). Gaps in knowledge are identified and where possible rough orders of cost are estimated. The group is conscious of the pitfalls of producing a report that would be difficult to read and understand because of the many complex scientific issues that must be addressed. Therefore, the main body of the report addresses the major concepts and culminates in conclusions and recommendations. Technical issues are addressed in annexes prepared by some of the specialists who were co-opted onto the group.

DEFINITIONS OF SCREENING

2.1 The term 'screening' can be used with different meaning in different situations:

a. The term is widely used within the Department of Health. The NSC's definition of screening is:

> ‘a public health service in which members of a defined population, who do not necessarily perceive they are at risk of, or are already affected by a disease or its complications, are asked a question or offered a test, to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risk of a disease or its complications.’

b. Within colloquial use the term can be used less specifically to mean the application of any medical test with the aim of achieving a diagnosis.

c. Within the field of occupational health, the term is occasionally used as a synonym for ‘biological monitoring’. The Health and Safety Executive define this as:

> ‘the measurement and assessment of chemicals or their metabolites in exposed workers’.

2.2 It is therefore essential that, when the term is used in scientific discussion it is exactly defined. For the purposes of this report, which has been compiled according to the terms of reference for the group and which aims to address appropriate screening tests for military exposures to DU, the following definitions have been set:

a. *Population Screening*: this is the application of a suitable test that can be offered to any individual (Serviceman, ex-serviceman or civilian employee or ex-employee of MOD) who is concerned that previous exposure to DU may have affected his or her health. Two types of screening test are considered under this definition:

(1) Screening tests to assess and quantify retrospective exposure by direct or indirect measurement of uranium/uranium isotopes.

(2) Screening tests to detect disease caused by uranium.

b. *Occupational Screening*: this is the application of suitable tests for the prospective assessment of occupational exposure. This is synonymous with the HSE definition of ‘biological monitoring’.

c. *Medical assessment*: this is a system of medical consultations and medical investigations to assess illness and disease in an individual, tailored to the needs of that individual. It is not considered to be a type of screening.

d. The term health screening has not been used within this document since ambiguity surrounding the use of this term has been found to confuse the distinction between tests suitable for population screening and tests suitable for medical assessment.

AIMS OF THE REPORT

3.1 The report aims to provide advice on the availability, suitability and development of screening tests for use in population screening and occupational screening. The report does not consider medical investigations that may be appropriate for medical assessment of an individual.

3.2 When considering the suitability of different screening tests, it is important to recognise that they only form a single part of screening programmes. Individuals attending for screening need to be given sufficient information to enable them to make an informed decision as to whether to undergo a screening test and the results must be explained to

them so that they understand their significance. The group has not considered it possible to advise about the merits of specific screening tests without knowledge or foresight of how these tests are intended to fit within their respective programmes. Therefore to enable constructive advice to be given at this stage, this report has aimed to advise about the suitability of screening tests placed within outline screening programmes, rather than addressing screening tests in isolation.

SCIENTIFIC BACKGROUND

The hazards associated with DU munitions

4.1 Uranium is a naturally occurring element that is present in rocks, soil, air, water, plants and animals. All humans absorb natural uranium from food and drink, retain some within their bodies, and excrete some in urine and faeces.

4.2 Natural uranium is radioactive, it has three main isotopes that emit alpha particles at different rates. These particles have little penetrating power so natural uranium is predominantly only a hazard when inside the body. It is also a heavy metal that presents a chemical hazard.

4.3 Depleted uranium is elemental uranium that has the same three main isotopes that are present in natural uranium, they are just present in different proportions. Since there is more of the isotope with the lowest decay rate and less of the two others, depleted uranium is 40% less of a radioactive hazard than natural uranium. Depleted uranium is also a heavy metal that presents a chemical hazard. As the chemical properties of an element are based on the number of protons that define the element and since all the isotopes have by definition the same number of protons, the chemical hazard presented by depleted uranium is identical to that presented by natural uranium.

4.4 In the military setting the main hazard from DU (apart from shrapnel) is the inhalation of an aerosol of the relatively insoluble oxides which form when a DU round strikes its target. Only personnel in the vicinity of the target, at the time of the strike, would be affected. A lesser risk exists if personnel enter damaged vehicles or contaminated areas at a later date and disturbs any DU dust that has settled out on surfaces. The re-suspended dust may be inhaled if the appropriate respiratory protection is not worn. Another possibility is that wounds may be contaminated. The risks from ingestion are much smaller but should not be neglected.

The risk of ill-health effects

4.5 The health risks associated with such intakes of DU are well understood and have been extensively reviewed in a series of internationally published reports[4, 5, 6]. These reviews have considered the evidence for a causative association between uranium or depleted uranium exposure and diseases such as cancers that might be expected to

[4] Gulf War and Health Volume 1 Chapter 4 Depleted Uranium. C Fulco, C Liverman, H Sox. Committee of Health effects associated with exposure during the Gulf War, Institute of Medicine of the US National Academy of Sciences, Washington DC.

[5] BEIR IV (1998), Health risks of radon and other internally deposited alpha-emitters. Committee on the Biological Effects of Ionizing Radiations, National Research Council, Washington, D. C., National Academy Press.

[6] Agency for Toxic Substances and Disease Registry (ATSDR), U. S. Department of Health and Human Services, Toxicological Profile for Uranium, (1999).

show an increased incidence following exposure to a radioactive hazard. They have also considered the evidence for a causative association between uranium or depleted uranium exposure and diseases that may be caused by the chemical hazard (such as kidney disease which is a known effect following exposure to other heavy metals).

4.6 Essentially, at cumulative dose levels lower than 200milliSieverts (mSv), there is limited/suggestive evidence of *no* association between exposure to uranium and the following health outcomes: lung cancer or clinically significant renal disease. This dose roughly corresponds to the burden occurring from a full year's exposure to a dusty indoor uranium workshop environment[7] and is far in excess of any exposure envisaged in the worst battlefield conditions. There is insufficient evidence to determine whether an association does or does not exist between exposure to uranium and a range of other health outcomes[1].

4.7 The clinical follow up programme for US Gulf veterans has reported no evidence of ill health effects related to DU exposure in these veterans[8].

4.8 In all these reports the overriding conclusion seems to be that ill health effects can not be positively excluded but, conversely, there is no proven mechanism linking DU exposure to increased mortality or specific ill-health effects. Therefore any risks that may exist in the military setting are, on the whole, likely to be insignificant, or acceptably small.

Technical aspects of screening programmes

4.9 Population screening programmes can have health benefits by detecting disease early to allow prompt treatment to begin. However these programmes are never foolproof and there are risks involved. In any screening programme, there is an irreducible minimum of false positive results (wrong reports of having a condition) and false negative results (wrong reports of *not* having a condition); both cause harm. False positives lead to physical harm from inappropriate treatments, psychological harm from anxiety and social harm through inappropriate labelling with ill health. False negatives lead to inappropriate reassurance and potential acceptance of risk behaviour that would otherwise be avoided. Programmes and tests that correctly identify true positives are termed ‘highly sensitive’. Programmes and tests that correctly identify true negatives are termed ‘highly specific’.

4.10 This concept that screening programmes can cause harm has nor been readily understood by the public and negative feedback such as unhelpful media attention has further reduced the effectiveness of some programmes. To achieve the change in public perception required to minimise harm the NSC is increasingly presenting screening as means of ‘risk reduction’ and emphasising the point that although screening programmes aim to benefit populations as a whole, some individuals will be harmed since no programme is foolproof. They are also introducing the concept of ‘informed choice’ leading to an 'invitation to be screened' into screening programmes. The Second Report of the UK National Screening Committee explains this concept in detail. (Enclosure 1)

4.11 To assist in the development of screening programmes that do more good than harm the NSC gives advice that an appropriately constructed programme will build around a framework of:

a. A process of public education.

[7] Mc Diarmid M A. Depleted uranium and public health. BMJ No 7279 20 January 2000
[8] Mc Diarmid M A. Keogh JP, Squibb KS, Kane R et al. Health effects of depleted uranium on exposed Gulf War veterans. Environ Res 2000; 82: 168 - 80

b. Well designed questionnaires.

c. Informed consent.

d. Appropriate medical consultation.

e. The careful selection of an analytical test.

f. The appropriate interpretation of that test.

g. A plan for managing positive results.

h. A policy for epidemiology study.

i. A support programme for participating doctors.

j. A system of audit.

4.12 In order to appraise the viability, effectiveness and appropriateness of a screening programme the NSC have also set down criteria against which a programme can be evaluated. The criteria are based around the specific medical condition, the screening test, the treatment for the condition and the screening programme as a whole. A full description of the criteria is at Appendix C to the UK National Screening Committee Second Report (www.doh.gov.uk/nsc/library/pdfs/secondreport.pdf)

CHOICE OF SCREENING TESTS

Relevant criteria

5.1 A wide range of tests could be suggested for various types of screening and a wide range of factors determine the suitability of one particular test for one particular programme. The most relevant criteria that need to be considered are discussed in the following paragraphs.

5.2 Validity.

a. Test validity.

(1) The test should actually measure what it is intended to measure.

(2) The distribution of test values in the population to which the test is to be offered should be known so that suitable action levels can be set to guide treatment and management using the results of the test.

b. Sampling and laboratory validity. Even if a test method is valid, a whole range of quality control procedures need to be in place to cover the sampling and laboratory procedures to ensure that any tests conducted for a programme are valid. Such measures are essential to minimise the harm that will arise from false positive and false negative results. Issues of sampling and laboratory validity are dealt with in detail in Annex B.

5.3 Test precision. The test should be ‘precise’. This means that it should not give many false positive or false negative results.

5.4 Safety, acceptability, cost and availability. These are all other factors that need to be considered. Safety is of prime importance since any inherent risks from the test procedure may significantly affect the risk/benefit analysis of the effectiveness of screening. Non-invasive procedures are preferred; for this reason, when biological samples are required, urine is preferred to blood.

Tests to assess Uranium/DU exposure

5.5 Tests to assess uranium/DU exposure could have a place in both population screening and occupational screening programmes. A wide range of tests can be used to detect uranium and its isotopes in biological samples. Direct tests, such as urine analysis by mass spectrometry, measure uranium and/or its isotopes by direct detection in a sample. Indirect tests, such as whole body monitoring, make calculations by other means.

5.6 Each test that is capable of detecting uranium and/or its isotopes can be assessed to determine its suitability for use in any particular screening programme by using the factors discussed in the section above. The International Commission on Radiological Protection (ICRP) has also issued guidance on the means by which intakes of uranium may be assessed[9, 10]. These methods include *whole body monitoring* and *faecal* and *urine analysis*. ICRP have also developed sophisticated biokinetics models for uranium and the use of these models has been endorsed by the MOD, Trades Unions and other participants in the UK Nuclear Industry Compensation Scheme.

5.7 Annex C provides expert comment on the merits of a range of tests that use different methods and different biological samples. However, for the purposes of population and occupational screening, MOD should accept the advice of the IRCP and use established techniques in any screening programme. This will avoid the costs and delays that would result from trying to accredit some of the more esoteric forms of biological monitoring such as analysis of blood or hair. However MOD should also continue to monitor developments in this area.

Whole body monitoring

5.8 Whole body monitoring is the name given to the identification and measurement of radiations emitted from within the body and gives information on the nature and quantity of radioactive materials within the body. Lung monitoring is the term given to a particular type of whole body monitoring that focuses on the detection of material within the lungs. Two main factors significantly limit the utility of these techniques as a screening test for DU. The energies from DU are very difficult to detect because it is mainly an alpha emitter and the technique is highly dependent on the time between intake and monitoring.

Faecal analysis

5.9 Faecal monitoring is unsuitable for use as a screening test. It is only an appropriate technique to assess large, acute exposures soon after exposure.

Urine analysis

5.10 It is tests to measure the urinary excretion of total uranium or uranium isotopes that are potentially most suitable for use in population and occupational screening programmes.

[9] ICRP 54: Individual Monitoring for Intakes of Radionuclides by Workers: Design and interpretation.
[10] ICRP 78: Individual monitoring for internal exposure of workers

5.11 The use of urine samples as biological specimens for monitoring is generally acceptable to the public, it is non-invasive and, as mentioned above, the suitability of the technique has been recognised by the ICRP. However there is no standard method for detecting uranium (or the concentrations of uranium isotopes) in urine. Each laboratory has developed equipment that meets its own specific needs and there is often some overlap between techniques. There are also significant limitations to the use of the method as a whole.

5.12 Details of tests for urinary uranium are given some of the following paragraphs. However, the information presented is extremely simplistic and supplied as a rough guide only. Examples given are for illustrative purposes only. Since laboratories have developed their own equipment and methods, the variety of tests, test capabilities and test limitations are actually much wider than portrayed here. Much further work is required to determine the exact cost, availability and capability of the various tests for urinary uranium, including detailed consideration of their limitations before any conclusions can be drawn about choice and the overall suitability of any one test for a particular screening programme.

5.13 Key points:

a. Since it is exposure to DU rather than total uranium that has lead to the requirement for DU screening, tests to identify specifically DU would ideally be more appropriate that tests for total uranium.

b. For screening purposes, the practical difference between natural and depleted uranium is in the uranium-235/uranium-238 ratio. The actual difference between these ratios is just a fraction of a percent. Natural uranium contains approximately 0.7% U^{235} and 99.2% U^{238}, whereas DU contains approximately 0.2% U^{235} and 99.7% U^{238}. Since natural uranium is already excreted in urine, the identification of minute changes in isotopic ratios that occur when DU is mixed with natural uranium is a significant technical challenge. Additionally, because of limitations in analysis equipment which will always be present no matter how far scientific techniques advance, there will always be a level at which an altered ratio will not be detectable. Therefore it is never possible to state that absolutely no DU is present in a sample.

c. DU is gradually eliminated from the body after intake. If a urine analysis has determined the concentration of DU present in the sample, an estimate of DU exposure can be made through the use of the ICRP biokinetics models. However the procedure is complicated as there are several variables to be considered. These include the size of the intake, whether an exposure is chronic or acute and the time between intake and assessment. Intakes become more difficult to detect as the size of the intake decreases and as the time between the exposure and the assessment increases. Even the most sophisticated tests will be unable to exclude DU exposure if excretion of DU during the lag time between exposure and testing has reduced its concentration within the urine to below detectable levels. This also contributes to the impossibility of stating that absolutely no intake of DU has occurred.

5.14 Tests for uranium isotopes.

a. Thermal Ionisation Mass Spectrometry (TIMS)

(1) This laboratory technique is used in research facilities involved in geochemistry work. It is one of the most sophisticated forms of uranium isotope analysis available anywhere in the world and it can quantify

smaller uranium isotope concentrations more than any other form of test in regular use. However as yet the technique still has to be validated for use in biological specimens such as urine.

(2) If the test can be validated it would be the gold standard test against which all others would be judged. It would be the only test able to detect a small DU exposure that occurred years ago. For illustration, it would probably be the only test able to detect exposures that were smaller in dose or longer ago in time than an 8mg intake of DU that occurred about 2 years earlier. It would probably be able to detect DU if it constituted just 5% of the total urinary uranium excretion, perhaps just about able to detect a 1mg DU exposure that occurred 10 years ago. It would not be able to exclude exposures to DU smaller than this.

(3) The test would probably require a 24 hour collection sample, it would be expensive (it is currently about £350 for a single specimen), and the limited facilities available would probably be unable to cope with large numbers of samples. Work to identify laboratories that might carry out this type of work and their capabilities in terms of accreditation and sample throughput is in progress. However it is known that laboratories carrying out the more sensitive forms of uranium analyses do not usually have any form of accreditation and it would therefore also be necessary to initiate a laboratory inter-comparison.

b. <u>High Resolution Inductively Coupled Plasma Mass Spectrometry</u>

(1) This laboratory technique is validated for analysis of urine samples. For illustration, its limit of DU detection in urine would be when the DU concentration was about one and a half times that of the background natural uranium. This would probably equate with an 8mg intake of DU that occurred about 2 years earlier and it would probably not be able to exclude exposures to DU smaller than this.

(2) This test can be performed on a 30ml ‘spot’ sample of urine and it is currently available in at least one accredited laboratory for about £100 per specimen.

5.15 <u>Tests for total urinary uranium only.: **I**nductively Coupled Plasma Mass Spectrometry.</u>

a. This laboratory technique is validated for analysis of urine samples but it can not specifically detect or quantify DU exposure. This is its main weakness. Interpretation of test results is complicated because:

(1) The amount of natural uranium excreted by the body depends on geographical location and diet and only very limited information is available on the normal range. What information there is suggests that typical urinary uranium levels in the UK probably range between 10 and 35 nanograms per litre but the full range of normal urinary uranium levels is probably much wider than this.

(2) It is not known how an individuals normal urinary uranium excretion may change during and after a deployment overseas where exposure to natural uranium in the environment, food and water may be different to that in the UK.

b. The test can be performed on a 30ml 'spot' sample of urine and it is currently available in accredited laboratories for about £40 per specimen.

c. If the normal range of urinary natural uranium excretion is determined more precisely, then this test could have a practical role in some types of screening programme. It could not be used where there is a specific need to detect or quantify DU exposure but it could allow some conclusions to be drawn about possible levels of risk. This could be done by using a pragmatic decision to assume that all the uranium detected in a sample (or perhaps all the uranium detected above a certain level such as the median excretion of normal background natural uranium) is DU.

d. By making such an assumption, and accepting its limitations, this could allow this test to be used as a cheap initial screen for depleted uranium in a tiered programme of testing. For example if an 8mg intake of DU occurred about 2 years earlier this would probably result in an increase in the total uranium excretion by an extra one and a half times the normal background natural uranium excretion (based on the limited information available at present). This high level of excretion, above the background natural uranium excretion, would be detected by this test. Further analysis by high resolution inductively coupled mass spectrometry would then be able to confirm whether the high level of uranium excreted actually contained DU; this is the rationale being used in the current U.S. voluntary screening programme for DU exposure (Annex D).

Conclusion

5.16 Tests to measure the urinary excretion of total uranium or uranium isotopes are potentially the most suitable for use in population and occupational screening programmes.

5.17 Much further work is required to determine the exact cost, availability and capability of the various tests for urinary uranium before any conclusion could be drawn about choice and the overall suitability of any one test for a particular screening programme.

5.18 No tests can absolutely exclude DU exposure.

5.19 There is the potential for a gold standard technique of Thermal Ionisation Mass Spectrometry to be developed and validated for the assessment of uranium isotopes in urine in the future.

5.20 Other less sensitive tests for DU exposure are already available but have various limitations.

5.21 Ultimately the choice of a screening test must depend on how well it enables a full screening programme to address its aims. Further discussion about choice of test therefore follows in the main sections that each deal with a different type of screening programme.

POPULATION SCREENING

PART 1: SCREENING TESTS TO ASSESS AND QUANTIFY RETROSPECTIVE EXPOSURE BY DIRECT OR INDIRECT MEASUREMENT OF URANIUM/URANIUM ISOTOPES

6.1 The achievable aims of population screening programmes that use different types of screening test are different. Screening tests/programmes to assess and quantify retrospective exposure by direct or indirect measurement of uranium/uranium isotopes are

discussed in this section. Screening tests/programmes to detect disease caused by uranium are discussed in the next main section entitled 'Population Screening Part 2'.

Discussion

6.2 A laboratory test giving some assessment and quantification of retrospective exposure to a hazardous chemical can sometimes be used to quantify the increased probability of adverse effects developing as a consequence of exposure. In the case of DU, exact quantification of this risk is difficult. Taking all the evidence into account the risk is likely to be low but not zero. However as yet there is insufficient evidence to conclude that there is a causal relationship between military DU exposure and any specific medical condition.

6.3 The NSC criteria, on which the effectiveness of a screening programme can be evaluated, consider a specific condition first and only then examine whether the epidemiology of the condition is adequately understood, whether there is a detectable risk factor and whether the condition has a latent period or early symptomatic stage.

6.4 A risk factor is being identified with the assessment of DU exposure, but the exact nature of the resultant risk can not be associated with a specific medical condition. No assessment of latency or early symptomatology under the terms of the criteria can therefore be made. Similarly there can be no assessment of whether early treatment improves the eventual outcome.

6.5 Taking these factors into account, any screening tests/programmes to assess and quantify retrospective exposure by direct or indirect measurement of uranium/uranium isotopes will be unable to meet most of the appraisal criteria set by the NSC. However after considering the NSC's advice as a whole there may still be merit in establishing a programme.

6.6 Within the boundaries of current scientific knowledge, there is no active treatment to reduce the risk of ill-health caused by DU that could be offered to individuals who undergo the screening test and have their exposure quantified. However assessment of their exposure combined with individual risk assessment communication and further education about control measures to minimise exposure in the future are likely to be valid interventions to reduce the harm caused by concern over DU.

6.7 The radioactive properties of DU enable an estimate of risk from the radiation hazard posed by DU to be calculated. Using biokinetic models for uranium that have been developed by the International Commission on Radiological Protection (ICRP) the test result could be used to provide an estimate of radiation dose (in milliSieverts) that has been received from the DU exposure. Risks from the stochastic effects of radiation (i.e. the late effects such as cancer that arise by chance in a proportion of exposed personnel) can then be quantified.

6.8 Estimation of the risk posed by the chemical toxicity of uranium is difficult to quantify since epidemiological studies have not been able to establish a causative association between uranium exposure and any specific medical condition. Nevertheless quantification of exposure and comparison of exposure to other accepted occupational and day to day hazards may enable concerned individuals to view their exposure with less concern.

Aims and objectives

6.9 The specific aims and objectives of a population screening programme based on the use of a test to assess and quantify exposure could therefore be to:

a. Demonstrate MOD's commitment to listen and to care for its personnel.

b. Address the fears, anxieties and concerns of all MOD personnel who:

(1) Want to know if they have been exposed to DU.

(2) Want their exposure quantified.

(3) Want adequate explanation of their personal risk of ill health following their exposure.

c. Educate, inform and reassure MOD personnel about the nature of the hazard, the risks, and the effectiveness of standard control measures (such as establishing cordons and using respiratory protective equipment).

d. Offer an exposure assessment which includes a laboratory test to the most concerned personnel.

6.11 Suitable test

a. One may think that the fundamental question that a participant in a population screening programme will ask is,

'What is my personal risk of ill-health from potential exposure to DU?'

b. However, in the climate of fear in relation to the potential ill-health effects produced by DU produced by alarmist statements made by pressure groups and intense media interest, concerned individuals may not develop their thoughts to conclude with this fundamental question. Instead they may initially demand answers to more basic questions such as,

'Do I have *Depleted Uranium* in my body?'
'If so, how much?'

c. Only once they feel this exposure has been quantified may they then move on to consider their personal risk of ill health.

d. On this basis a suitable population screening test to assess and quantify retrospective exposure to DU is more likely to be acceptable to concerned individuals if it is capable of differentiating *depleted* uranium from the *natural* uranium which is normally present within the body. However every concerned individual still needs to accept that no matter how sensitive or advance a test is used, no test can absolutely exclude DU exposure.

e. A test for total uranium could be used perhaps with an action level set to trigger further investigation by a test to detect uranium isotopes. However pressure groups may question assumptions about background exposure and they may continue to demand a specific test for DU for all.

On the basis of the conclusions in the main section entitled 'Choice of Screening Tests', a test of urinary uranium or uranium isotope excretion may be suitable for this sort of screening programme. However a more detailed appraisal of the urine tests that are potentially available is required.

Outline methods

6.12 The programme would need to be publicised widely. This publicity should address a substantial number of concerns. The written publicity about the programme would need to include:

a. Information about the nature of the hazard, the risks, and the effectiveness of standard control measures. It should be frank that the risk of ill-health after exposure may not be zero but is likely to be low and well below other risks usually considered acceptable when undertaking employment.

b. That the programme is open to anyone.

c. A description about the test or tests available and the capabilities of these test/tests.

6.13 Access to the testing part of the programme would be by appointment at a Medical Centre or Occupational Health Department. The need for appointment and attendance would act as a natural filter to select the most concerned. At the appointment:

a. A questionnaire would need to be administered by a medic or nurse. It would include questions on exposure and open ended questions about symptoms.

b. The pros and cons of a screening test including the risk of harm from false positive results would be explained. Informed consent for testing would be sought.

c. An appropriate urine specimen would then be taken in line with a sampling protocol.

6.14 The urine would be analysed using a test chosen on the results of pre-programme development. There may be requirement for repeat specimens to exclude contamination if initial analysis detects high levels of uranium.

6.15 Individuals would be counselled about their result by appointment with their unit medical officer, general practitioner, or occupational health physician. Guidance information would be required to assist in the interpretation of the results and risk communication.

Further work required

6.16 Pre-programme development:

a. A very substantial amount of work, including the pivotal task of identifying an appropriate test for urinary uranium isotopes and validating its use in this sort of programme, is required to develop this outline programme before it can safely be introduced.

b. A project team needs to be established to develop and validate the methodology as soon as possible. The NSC foresees the requirement for a workshop to discuss potential laboratory screening tests. Interested parties could be invited (the Veterans Associations, the Royal British Legion, manufactures of mass spectrometers, laboratories with professed expertise etc.).

c. All stages within the programme such as the questionnaire, sampling protocols, and the laboratory test need to be examined independently. It may be appropriate to use a group of unexposed, unconcerned volunteers to provide urine

samples to develop the protocols for sampling and testing. Use of veterans at this stage could be inappropriate.

d. There needs to be assessment of the likely demand for the test. This needs to be linked with a study of the availability of suitably accredited laboratories to conduct the test.

6.17 External validation. Once pre-programme development is complete, the suggested programme should be offered to the NSC for final independent scrutiny. The NSC have advised that a well-researched Population Screening Programme could take some 9 months to construct and would not endorse the introduction of a screening programme if it was not thoroughly researched.

Pilot Group.

6.18 Before the programme is introduced fully, it should be run on a pilot group. This allows some assessment and validation of the programme as a whole. Minor faults and omissions can then be rectified for the benefit of the majority.

PART 2: SCREENING TESTS TO DETECT DISEASE CAUSED BY URANIUM

7.1 The achievable aims of population screening programmes that use different types of screening test are different. Screening tests/programmes to detect disease caused by uranium are discussed in this section. Screening tests/programmes to assess and quantify retrospective exposure by direct or indirect measurement of uranium/uranium isotopes were discussed in the previous main section entitled 'Population Screening Part 1'.

Discussion

7.2 The NSC criteria, on which the effectiveness of a screening programme can be evaluated, consider a specific condition first and then examine whether the epidemiology of the condition is adequately understood, whether there is a detectable risk factor and whether the condition has a latent period or early symptomatic stage detectable by a simple, safe, precise, validated screening test. Consideration is also required of whether early treatment of individuals detected by the programme improves their eventual outcome before a final decision about the appropriateness of a screening programme can be made on the basis of a risk/benefit analysis.

7.3 In the situation of military exposure to DU, it is appreciated that an exposure to DU could be associated with a low risk of adverse health effects. However as yet there is insufficient evidence to conclude that there is a causal relationship between military DU exposure and any specific medical condition.

Conclusion

7.4 In the absence of an established causal relationship between military DU exposure and any specific medical condition, it is the group's opinion that a population screening programme for DU using a test to detect disease caused by uranium is not appropriate.

7.5 This will remain the case indefinitely unless future epidemiological research establishes a causal relationship between DU exposure and a specific illness or disease.

OCCUPATIONAL SCREENING PROGRAMME

Aims and objectives

8.1 The occupational screening programme for DU has been defined as the application of suitable tests for the prospective assessment of occupational exposure. It is synonymous with biological monitoring. The aims and objectives of this type of programme would therefore be to:

a. Assess the adequacy of control measures already in force to minimise exposure to DU.

b. Gain data to inform the risk assessment process.

c. Reassure MOD personnel that every measure is being taken to ensure that exposure is minimised by the use of appropriate controls and that the residual risk of ill health following whatever minor exposures that occur is minimal.

Discussion

8.2 The need for a population screening rest for DU has arisen because personnel who have been potentially exposed in the past have become concerned that they may now be at more risk of adverse health effects than they realised at the time of exposure. This may either be because they now believe that DU is more hazardous than they were told or because that they were exposed to more DU than they expected. In effect they do not trust that the risk assessment for their DU exposure was correct. Population screening is now being considered as a means of addressing the concerns that have arisen.

8.3 The key difference between an occupational screening programme and a population screening programme is that an occupational screening programme is concerned with *prospective* exposure to DU. An occupational screening programme will provide some assurance that a risk assessment for DU exposure is correct. However other procedures such as the occupational hygiene assessments done by environmental monitoring and personal monitoring also have key roles to play. The role and function of an occupational monitoring programme must therefore be considered alongside other procedures that inform and assure the risk assessment process.

Suitable test/tests

8.4 On the basis of the conclusions in the main section entitled ‘Choice of Screening Tests’, a test of urinary uranium or uranium isotope excretion may be suitable for an occupational screening programme. However a more detailed appraisal of the urine tests that are potentially available and their likely effectiveness in an occupational screening programme is required.

8.5 Since an occupational monitoring programme will be concerned with prospective exposures to DU, individuals should be briefed about the hazards to which they may be exposed as part of their work, the risks posed by the hazard and the control measures in place to minimise exposure. During this process of education and training individuals will need to accept that, although an exposure may occur, proper controls should minimise the risk of harm. If this process of risk communication is effective there should not be intense pressure to provide a test that detects DU specifically if a test of total uranium can justifiably determine that exposure to DU above an acceptable level has not occurred. Nor should there be a need to utilise a test with an ability to detect levels of exposure that are below a threshold which is deemed acceptable in advance. If any test results revealed that a

threshold had been exceeded then a suitably validated test of uranium isotopes could qualify if the result was due to DU exposure or increased excretion of natural uranium.

Outline methods

8.6 General advice about setting up and managing a biological monitoring programme including advice about some technical aspects is available from the HSE[11]. The following paragraphs outline a suggested method of military DU biological monitoring that should be considered alongside any appraisal of the suitability of a particular type of screening test.

8.7 Populations to be enrolled in the programme need to be selected using an assessment of their risk of future exposure to DU. This needs to be balanced against the risk of ill health following exposure, the capability and costs of the programme and the risk of physical, psychological or social harm from false test results. Depending on the assessment, the populations chosen could vary from the most inclusive such as all personnel deployed on an operation to the very specific such as EOD teams, bomb damage assessment teams or MOD munitions workers with potentially significant DU exposure.

8.8 A voluntary programme designed to encourage high levels of participation amongst the target population, rather than an obligatory programme, is probably most appropriate. Issues to consider in any debate include:

a. An ethical need to obtain an individual's informed consent before conducting a test.

b. The consequences of failures to consent.

c. The fact that the risk of harm following likely exposures is thought to be low.

d. The fact that although the tests are non invasive, there are risks of psychological and social harm as in any screening programme.

e. The need to take pre-deployment samples to provide a baseline.

8.9 Medical aspects of the programme would be run from an Occupational Health Centre/Medical Centre. At an initial appointment:

a. A questionnaire would need to be administered by a medic or nurse. It would include questions on the potential for previous exposures and relevant questions about past medical history.

b. Informed consent for testing would need to be sought. The pros and cons of a screening test would be explained. These would include advantages such as the assurance gained by the evaluation of control measures and disadvantages such as the risk of harm from false positive results. There needs to be clear advice about the actions that would be taken in the case of a high result. On the basis of current knowledge it would be inappropriate to stop an individual deploying or working but it would be appropriate to reinforce his knowledge of appropriate control measures.

c. An appropriate urine specimen would then be taken in line with a sampling protocol.

[11] Biological monitoring in the workplace: a guide to its practical application to chemical exposure. Health and Safety Executive. London, Sheffield. HSE 1997 2nd ed.

8.10 The urine would be analysed for either total uranium or uranium isotopes. The exact test chosen to form the backbone of the programme would depend on the results of pre-programme development. There may be requirement for repeat specimens to exclude contamination if initial analysis detects high levels of uranium.

8.11 After deployment, or a time in work where there may have been exposure to DU, individuals would return to complete another questionnaire seeking details of potential exposures including time, job, closeness to source, use of respiratory protection etc. A post exposure urine specimen would be required for appropriate analysis.

8.12 Individuals would be counselled about their result by appointment with their unit medical officer, general practitioner, or occupational health physician. Guidance information would be required to assist in the interpretation of the results, risk communication and the requirement for further actions or investigation. Flow charts may be required to assist this process especially if a test of total uranium is chosen during the stage of pre-programme development.

8.13 If the monitoring shows that individual exposures, or groups of exposures, have occurred that are above levels that are either expected or acceptable a health and safety investigation of the circumstances of exposure is required. Information from this assessment should be used to augment the risk assessment for DU and adjust the controls in place to minimise its exposure.

Further work required

8.14 Pre-programme development

a. A very substantial amount of work is required to develop a programme of occupational screening, using an appropriate test or combination of tests, before it can safely be introduced.

b. A project team should be established to develop and validate suitable methods. All stages within the programme such as the questionnaires, sampling protocols, and the choice of appropriate urine tests need to be examined independently. It may be appropriate to use a group of unexposed, unconcerned volunteers to provide urine samples to develop the sampling and testing protocols and techniques.

8.17 External validation. Once pre-programme development is complete, the suggested programme should be offered to external bodies for scrutiny and validation. The group considers that this should be obtained through the auspices of the Faculty of Occupational Medicine of the Royal College of Physicians. The NSC is of the opinion that an Occupational Screening Programme falls outside the scope of their jurisdiction and that the NSC screening criteria does not apply.

8.18 Pilot group. Before the programme is introduced fully, it should be run on a pilot group. This would allow some assessment and validation of the programme as a whole. Minor faults and omissions can then be rectified for the benefit of the majority.

OTHER CORE TECHNICAL ISSUES

9.1 This section discusses some core technical issues that must be addressed if the above programmes are to be developed and implemented.

Formation of a specialist group to manage the screening programmes

9.2 A project team is required for the pre-programme development of the population and occupational screening programmes. After the programmes are developed, a specialist group will be required to assess the results of the pilot studies and manage the programmes accordingly. The programmes need to be kept under constant review to ensure their continued suitability and effectiveness. The results of tests from the programmes need to be linked with environmental monitoring and other exposure data to update the risk assessment for work where exposure to DU may occur. The team would need to include medical, health physics, laboratory, statistical and epidemiological expertise.

Statistical and epidemiological considerations

9.3 The results of screening tests used within population and occupational screening programmes will be interpreted on an individual basis by medical staff advising personnel within the programmes. There is a specific need to include statistical and epidemiological interpretation of the results on a population basis. These techniques are essential to:

a. Establish and describe the normal background uranium and uranium isotope excretion in different populations.

b. Identify the probability with which small variations in uranium or uranium isotope around the levels of sensitivity of a laboratory test are likely to reflect a true result rather than test error.

c. Study and identify the differences in exposure between different groups of individuals. These findings would be used to inform the risk assessment for these groups.

Major Supportive Studies

9.4 Descriptive epidemiology

There is a need for descriptive studies to establish the normal background uranium and uranium isotope excretion in different populations and different circumstances so that the results of any tests can be explained and validated. Since there is a need to determine normal excretion data for a range of characteristics such as age, diet, gender and occupation, the studies required may have to actively recruit subjects who fit the characteristics required. As it is essential to ensure that subjects for this work have the minimal chance of having been exposed to DU in the past, both service and civilian subjects are likely to be required (it may be difficult to find servicemen in the older age groups who have had no potential DU exposure).

9.5 Analytic epidemiology

Subject to appropriate ethical approval, a special cross sectional study of retrospective exposures with active recruitment of subjects (rather than simple inclusion of volunteers from the population screening programme) could yield extremely valuable information to inform the risk assessment process. This study would require personnel to be identified who had recently performed duties where their potential exposure to DU could be categorised. These personnel could then have studies to assess their total uranium and uranium isotope excretion. Comparison of the results between the categories may allow some quantification of actual DU absorption during military operations.

CONCLUSIONS

10.1 Risk assessment and published data support the view that there is little, if any risk to ill health that can be attributed to DU exposure in the military setting but significant concern exists amongst Service personnel, civilians and their families.

10.2 The screening programmes need to provide reassurance to the people who have been exposed in the past or who may be potentially exposed in the future. In trying to achieve this objective MOD must not cause harm by introducing invalid programmes. A careful balanced judgement is required.

10.3 Independent views of the screening programmes are needed at an early stage.

10.4 The introduction of a stand-alone test will not provide reassurance. Any test procedure must form part of a comprehensive screening programme structured in such a way as to provide individuals with enough information to develop an informed decision about their participation.

10.5 No test can absolutely exclude DU exposure. Uranium in urine analysis is considered to be the best available option. The choice of particular test - total uranium or isotopic ratio testing - is a very complex subject requiring further detailed study.

10.6 Validated tests exist that will provide information on total uranium in urine levels. However, this type of test will not provide an answer to the fundamental question being posed by the potentially exposed. *How much DU is in my body?* The more complex, sensitive (and potentially expensive) test for isotopic measurements (TIMS) may eventually be able to answer this question.

RECOMMENDATIONS

11.1 The National Screening Centre and the Faculty of Occupational Medicine be invited to comment on this report.

11.2 The NSC be invited to convene a workshop to consider methods of testing for DU.

11.3 Once methods of assaying DU have been developed and quality control assured then the test(s) should form part of programmes for screening for DU exposure.

11.4 The programmes, including pre-programme development and pilot studies must be developed in a methodical manner in consultations with external authorities.

11.5 Core technical issues must be developed and brought into the programme e.g. a specialist group to oversee development and arrangements for epidemiological studies.

11.6 The Institute of Naval Medicine should be tasked with developing a method for analysing uranium in urine and then act as an inter laboratory comparator. (It has a heavy metal laboratory with ICPMS and is adjacent to DERA Radiological Protection Service.)

Annexes:

A. Terms of Reference of Expert Advisory Group
B. Important Analytical Issues.
C. The Detection Of Depleted Uranium (DU) In Biological Matrices
D. U.S. Screening Programme

ANNEX A TO
INM 252/122/1
DATED 31 JAN 01

TERMS OF REFERENCE EXPERT ADVISORY GROUP ON SCREENING FOR DEPLETED URANIUM

1. The Expert Advisory Group on Screening for DU is to report to SG.

2. The role of the group is:

   a. To identify a suitable population screening test for DU (e.g. urinary uranium) that meets the criteria for screening laid down by the UK National Screening Committee of the UK Departments of Health, for use on Servicemen, civilians and Veterans previously deployed to areas where there has been DU.

   b. If no such test exists, to advise whether such a test can be devised and what further work is required to develop such a test.

   c. Consider whether there is an occupational screening test available that would identify exposure to low doses of DU in Servicemen and civilians deploying to areas where DU is being, or has been, used. The group is also to advise on whether such a test could be used to support, or in conjunction with, the environmental monitoring programme.

   d. If no such test exists, to advise whether such a test can be devised and what further work is required to develop such a test.

   e. To advise on options for confirmation that any positive results arising from screening are specifically caused by DU.

   f. In all cases to consider what capacity exists to carry out such tests in the UK and highlight any serious shortfall in capacity or quality.

   g. To advise on any gaps in our knowledge that ought to be remedied.

   h. Where possible, to identify a rough order of costs.

3. To advise on the appropriate form of health screening with diagnostic testing provided where clinically indicated, in support of or in place of population and / or occupational screening. The Expert Advisory group does not need to address the administration or location of such a programme.

4. Membership.

Surg Cdre N E Baldock QHP FRCP FFOM	Medical Officer in Charge Institute of Naval Medicine
Surg Cdr D Brown MSc(OM) MSc(Rad Med) FFOM	Head of Submarine and radiation Medicine
Surg Cdr M Dean MRCGP MFOM	Assistant Chairman Naval Nuclear Reactor Panel (Medical)
Surg Cdr C R M Foster MRCGP AFOM	Submarine & Radiation Medicine Trainee 1
Mr R Brown BSc	Principal Health Physicist, Radiation Protection Adviser

Dr R J Pethybridge MSc PhD	Head of Statistics Division
Dr Shayer PhD	Toxicologist
Dr D Lewis PhD	Laboratory Technical Manager
Lt Col J P G Bolton MSc MRCGP MFPHM	Gulf Veterans Illness Unit
Mr M Phillips MSc CPhys M Inst Phys MSRP	Directorate of Safety Environment and Fire Policy
Dr D Irvine	Epidemiologist, Surgeon General's Department
In attendance	
Prof J A Muir Gray CBE DSc MD FRCP	Programme Director National Screening Committee
Corresponding Member	
Brig L Lillywhite MBE MSc MFOM	Surgeon General's Department

ANNEX B TO
INM 252/122/1
DATED 31 JAN 01

DEPLETED URANIUM SCREENING: IMPORTANT ANALYTICAL ISSUES.

Dr D Lewis PhD, Laboratory Technical Manager, Institute of Naval Medicine

Introduction.

1.1 Regardless of any other factors the quality of the data collected during uranium screening, and therefore the success of the programme as a whole, rests entirely on the quality of the uranium analysis. This is especially true because, unlike normal clinical laboratory tests, data must be produced at or near the limits of detection of the methods most likely to be used.

1.2 Assuming the analysis is placed with a contract laboratory it is essential that MOD audits the contractors work at all stages to ensure that the data produced has meaning. This does not compromise the independence of the data as auditing could be carried out by a third party. It would be better, however, if there was a MOD input from the project management group.

1.3 To confirm the quality of the contractor's analysis several important factors need to be considered. The most important of these are as follows:

a. A clear understanding is needed of what the analysis data aims to show is needed before work is started so that a clear statement of requirement can be written.

b. Good quality methods for sample collection and handling must be agreed between MOD and the contractor.

c. Evidence is needed of the ability of the laboratory to analyse urine samples as this is not straightforward.

d. Details of the methods proposed by the laboratories are needed in advance to ensure fitness for purpose. This must include quality control protocols and evidence of method validation.

e. Careful technical scrutiny of bids is required at the tendering stage.

f. A system for auditing of the laboratories should be agreed between MOD and the contractor.

The statement of requirement.

2.1 Contractors will presumably be expected to bid for work via the normal MOD tendering procedure. By the time tenders are invited from potential contractors considerable effort is required to ensure that the statement of requirement clearly identifies the aims of the screening programme. This needs to include a detailed performance targets for sampling and uranium analysis so that tendering contractors have a clear idea of the work they are bidding for.

2.2 There is a clear need for an intelligent customer to develop and carry out the work needed to write the statement of requirement. MOD as the customer should have a major input into this process and it would seem that the expert advisory group is well placed to take on this role. It may be useful to include in the group's role the right to visit and audit contractors' laboratories to investigate details of bids. This forms part of the system of auditing which is elaborated in section 6.

2.3 There are a number of important factors which at first sight could be considered of interest in the laboratory only, they are discussed in the sections below. If public money is to be spent wisely and good quality data is to be obtained from the programme the issues are of crucial importance.

Sample collection and handling.

3.1 Sample handling and collection is perhaps the most crucial part of the programme. If poor or inappropriate samples are collected or samples are handled poorly even the best laboratory analysis and statistical studies will produce poor quality data.

3.2 Current UKAS accreditation guidelines require that a sampling plan is written before any work is carried out on a project of this size. This is sound practice as it focuses attention on the requirements for sample collection and handling which could easily be overlooked. The end result is a document that all parties can use as a reference and which ensures all sampling is carried out to the same standard. It is recommended that a sampling plan is set up for this programme and is trialled at the pilot stage.

3.3 The following factors are important:

a. The laboratory in co-operation with MOD should produce a fully documented sampling plan. This should detail all aspects of sample collection and handling and should be adhered to at all times to ensure integrity of the samples and thus validity of the data.

b. The plan should give full details of the sample containers to be used together with details of any required sample preservatives. Sample preservation may be essential if samples are in transit for any length of time.

c. The plan should include full details of how and when samples are to be collected. This must include instructions on how to minimise sample contamination during collection, handling and transport which could lead to false positive results. This is important as the levels of uranium to be measured are extremely low and the smallest speck of dust entering the sample could easily invalidate the data collected. As a result it is likely that medical staff managing sample collection will require training in sample handling procedures for such critical samples.

d. The plan should include details on the labelling of the samples and any accompanying paperwork so that a fully traceable audit trail can be maintained.

e. The plan should include details of the packaging and hazard labelling to be used for the samples and should take into account IATA regulations on transport of hazardous materials by air if appropriate.

f. The plan should include details of the measures taken to ensure sample integrity, preservation and security in transit. The use of tamper evident sample containers is recommended to avoid malicious contamination of samples.

g. The plan should include details of the measures taken at the laboratory to ensure sample security and preservation prior to analysis.

Evidence of contract laboratory performance and details of methods.

4.1 It has been noted that tendering laboratories are unlikely to have accreditation for the methods they offer. This in itself may not be the problem that it first appears to be as there is much that MOD can include in the statement of requirement to ensure the suitability of the methods tendered. It is however most important that the tendering laboratories have a clearly documented quality system or are accredited for similar work. They should also be clearly aware of current methods of quality control and method validation.

4.2 The following key areas should be addressed during the preparation of the statement of requirement and ideally should be complete before laboratories tender for the work. If methods need to be developed during the pilot stage these key areas should be agreed between MOD and the contractor before the main programme is started. All of these topics should represent current best practice.

a. The tendering laboratory should be appropriately experienced and if not accredited to carry out the specific method offered should have a clearly documented quality system.

b. The offered method should be fully validated to prove performance at the uranium concentration of interest. The validation data should be available to MOD for inspection and should include proof of all steps of the method. Assuming ICPMS is the method of choice the validation data should include information such as:

(1) Tests of linearity.

(2) Effects of matrix components on the quantification of uranium.

(3) Details of any mass interference effects.

(4) Recovery data for reference materials.

(5) Performance of the method in terms of within and between run standard deviation.

(6) Limit of detection for each uranium isotope.

(7) A statement of the precision of the method with respect to uranium concentration.

(8) Details of tests carried out to ensure suitability of the proposed sample containers.

c. A fully documented procedure to be followed in the laboratory during analysis should be written and should be available to MOD for inspection.

d. This documentation should include at least the following:

(1) The range of applicability.

(2) The absolute limit of detection and lowest reportable uranium concentrations.

(3) A statement on method precision at the concentration(s) of interest.

(4) A statement of method uncertainty.

(5) A fully documented quality control protocol should be available to MOD for inspection. This should include at least:

i. Details of calibration and traceability of calibration standards.

ii. Details of the tests performed to confirm equipment operation.

iii. Maintenance protocols and records for critical equipment.

iv. A documented protocol for analytical quality control giving details of the reference materials used and their traceability. The protocol should also detail the frequency of their use in routine analysis. The minimum standard of quality control would be reference materials run at the beginning and end of each analysis but bearing in mind the critical nature of the analysis a greater frequency of quality control would normally be expected.

v. Full details of control charting techniques used and examples of the charts. The use of these techniques should be considered essential.

vi. Full details of all relevant external performance schemes.

e. Documented procedures for data handling and archiving should be available to MOD. These should include at least:

(1) Details of storage of primary data.

(2) Full details of all calculations and corrections applied to the primary data prior to reporting.

(3) Details of the validation of any spreadsheets and other data transformations used by the laboratory.

4.3 In addition to this further quality assurance steps may be needed. The UK blood lead monitoring programme from the 1980s shares some similarities with the proposed uranium screening programme. In both cases the requirement was for high quality data to reflect small differences in exposure accurately. In the case of the blood lead programme samples were analysed by one method and a proportion reanalysed by another method to confirm the results. A similar approach may be useful with DU screening via one of the following:

a. A second laboratory could re-analyse a proportion of the samples to confirm the original data or the main contractor could do the same using a second independent technique. This would however add considerably to the cost of the screening programme.

b. The Institute of Naval Medicine possesses an ICPMS which could be used to set up a quality assurance system to re-analyse samples analysed by the main contractor. This would be highly advantageous as it would establish a direct line of

communication between MOD and the main contractor and would ensure that quality problems were identified quickly and remedied without the involvement of third parties. This would be acceptable as the main data could be generated independently probably under the scrutiny of an accreditation body.

4.4 An interlaboratory comparison trial has been suggested. Whilst this is a good idea it should be noted that this approach has limitations and may need to be in operation for some time before benefits are seen. A trial of this type is complementary to normal quality procedures and is only of value if the participating laboratory has a rigorous programme of quality control.

Technical scrutiny of bids at the tendering stage.

5.1 It is clear that a considerable number of laboratories may bid for work in this programme. It is essential that the correct laboratory is chosen and that unsuitable laboratories are rejected at an early stage.

5.2 If as normal the returned bids are examined by a tender assessment panel it is essential that the panel has the technical and scientific skill to be able to distinguish between competent and incompetent bids. It is strongly recommended that the expert advisory group is closely involved in the tender assessment to ensure that only valid laboratories are chosen.

5.3 Previous experience in the role of technical tender assessor suggests that a tendering exercise of this type can take a minimum of several months to organise (i.e. up to a month to finalise the statement of requirement and advertise; a month for labs to put tenders together and a month for the tender panel to decide on the successful bidder). It is clearly the case that the tendering exercise will introduce a delay into the screening programme as rushing the process could lead to an incorrect choice of laboratory and justifiable complaint from those laboratories not chosen.

Auditing

6.1 The contract for the supply of analytical services may be long running and costly so it is essential that the MOD maintains control over the contractor. Despite the requirement for independence it is essential that the MOD retains its position as the customer and the laboratory retains its role as a supplier of a service. To assist in this the following steps are suggested as part of the statement of requirement:

a. The MOD retains the right, at any time, to visit the contracting laboratory to scrutinise QC records, analytical techniques, data handling and all other relevant aspects of the laboratory's work. This is essential to ensure that quality is achieved and maintained, it is not enough to assume that a laboratory will continue to produce valid data throughout the whole of the contract period.

b. It is also essential that MOD actually uses these powers and carries out these audits on a regular basis. It is suggested that an audit team is set up for this purpose based on the expert advisory group.

c. MOD must claim ownership of the primary data and ensure that the data analysis is carried out to appropriate standards. This is essential as it will show how the final reporting data has been calculated and will document all corrections that have been applied.

Conclusions

7.1 The analytical issues raised above are of great importance in the success of a trial of this type especially where exposure is historical and the required analysis approaches limits of detection. In anything other than a simple screen for current exposure the margin for analytical error is great and should be considered carefully at all points of the screening programme.

ANNEX C TO
INM 252/122/1
DATED 31 JAN 01

PROPOSED METHODS FOR THE DETECTION OF DEPLETED URANIUM (DU) IN BIOLOGICAL MATRICES

INTRODUCTION

1. The National Screening Committee (NSC) defines a screening programme as "a public health service in which members of a defined population, who do not necessarily perceive they are at risk of, or are already affected by a disease or its complications, are asked a question or offered a test, to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risk of disease or its complications"[1].

2. Retrospective analysis of DU does not fully satisfy the NSC's criteria of a screening programme since there is no apparent detectable risk factor, or disease marker associated with the alleged health problems following DU exposure.

3. Several techniques have been proposed and implemented for the biological monitoring of (or retrospective assessment of exposure to) uranium (U) compounds, each with varying degrees of success. Because of the unique chemical and radiological properties of U, these methods vary in their approach to detection and subsequent relevance to the proposed screening programme.

4. That exposure to an agent has occurred can be demonstrated by analysing its presence in body fluids, tissues, or whole organs. Such an approach will give a measure of the internalised dose but provide little information about the potential risk involved. For this reason it may be more helpful to look at the levels of specific markers of damage in easily accessible tissues. The presence of such markers may give an indication of the *biologically effective dose* of an agent. Similarly, detection of *early biological effects* at known exposure levels will give a more relevant indication of likely risk following contact with a known toxic agent, although, at this stage, there is no apparent link between DU exposure and adverse health effects.

5. When selecting an appropriate screening method several criteria should be considered. The technique itself should not cause any undue distress to the subject and should ideally be non-invasive. Sampling should be a relatively simple procedure requiring little technical knowledge, and the subsequent analysis of samples should be reproducible, cost-effective, and performed according to well established protocols. The storage and transport of samples should also be given consideration with respect to the likelihood of accidental or intentional contamination, and quality control measures should be implemented at every stage of the screening programme to ensure reliable data.

6. Proposed methods of U biomonitoring are reviewed, and their relevance to a military screening programme discussed in the following sections.

[1] *Second Report of the UK National Screening Committee (2000), Department of Health, London.*

TESTS

Analysis of urine

7. Mechanism of uranium excretion

a. Current opinion on the retrospective assessment of exposure to U compounds favours the determination of this metal in urine due to its characteristic route of excretion and the fact that urine collection is a non-invasive procedure. Indeed, the International Commission on Radiological Protection (ICRP) recommends urinalysis for the monitoring of exposed personnel, in conjunction with faecal analysis and lung monitoring[2, 3] (discussed later in this annex).

b. Having entered the systemic circulation, the pharmacokinetic properties of U mean that the bulk of these compounds are filtered at the renal glomerulus and rapidly excreted via the kidney, regardless of the route of uptake. It should be emphasised that this mechanism of excretion only applies to U complexes which have become solubilised in the plasma – insoluble particles (e.g. accumulated in the lung) will tend to be retained at their site of deposition and will have much longer biological retention times.

c. Of the most common U species present in plasma, approximately 40% of U is bound to transferrin, the remaining 60% being in the form of low molecular weight complexes. These low molecular weight complexes (e.g. bicarbonates) are filtered at the renal glomerulus and excreted in urine, whilst larger U-protein complexes will tend to remain in blood. As the smaller complexes are excreted, the U-transferrin complexes dissociate liberating free uranyl ions (UO_2^{2+}) which are then able to combine with bicarbonate and other ligands. In this way a continuous equilibrium is established between large U-transferrin complexes and smaller low-molecular weight complexes, leading to a rapid elimination of U by glomerular filtration (for a review see Leggett, 1989[4]).

d. As a result of these physiological processes, the kidney is by far the most pertinent organ to U toxicity. Following filtration at the glomerulus, low molecular weight U complexes (e.g. U-bicarbonate) pass along the proximal convoluted tubule, the lumen of which is lined with a prominent brush-border of microvilli. Along the proximal convoluted tubule there is a decrease in pH[5] which causes the U-bicarbonate complex to dissociate, liberating free UO_2^{2+} which may then interact with other complexing species in the filtrate, or with components of the luminal membrane.

e. Any U which remains complexed in the filtrate, and possibly a small proportion of free UO_2^{2+}, will rapidly pass into the bladder. The portion of filtered U which is excreted

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[2] *International Commission on Radiological Protection (1988), Individual monitoring for intakes of radionuclides by workers: design and interpretation, Annals of the ICRP, **19**(1-3), 1-315, (ICRP publication 54).*

[3] *International Commission on Radiological Protection (1997), Individual monitoring for internal exposure of workers, Elsevier Science, **27**(3-4), (ICRP publication 78).*

[4] *Leggett, R. (1989), The behaviour and chemical toxicity of uranium in the kidney: a reassessment, Health Physics, **57**(3), 365-383.*

[5] *Brobeck, J. R. (1979), Best and Taylor's physiological basis of medical practice, Tenth edition, Baltimore, Williams and Wilkins.*

in the urine will depend on the acidity of the filtrate and the concentration of bicarbonate present.

f. Uncomplexed UO_2^{2+} that is not excreted will tend to bind to specific sites on the luminal membrane (possibly at phosphate groups of phospholipids) where it may interfere with normal cell homeostasis causing cell death, or is taken up into the cytoplasm by endocytosis leading to accumulation and the subsequent formation of uranyl phosphate "needles"[6].

g. Following cell death, bound U may then appear in the urine as a result of sloughing of microvilli and/or dead cells. Paradoxically, following high levels of cell death, U-containing debris may "clog" the nephron such that lower levels of U are detected in the urine. It is therefore apparent that the rate at which U appears in urine will depend on the level and duration of initial exposure, and will also be influenced by the normal kidney function of the individual.

h. Since U excretion may be influenced in this way by the normal kidney efficiency of an individual (independently of U insult), it is recommended that where detected U levels in urine are disproportionately high, the analysis should also take into account renal function by the monitoring of suitable protein markers. Appropriate excretion products for the assessment of kidney damage include N-acetyl-glucosaminidase (NAG), β-2-microglobulin (bMG), albumin, and retinol binding protein; with bMG being a specific marker for U-induced renal disease[7].

8. 24 hour urine collection vs. "spot tests"

a. It is generally regarded that the most reliable data from urine analysis are obtained from samples collected over a 24-hour period and corrected for levels of creatinine excretion.

b. For practical reasons however, it may not always be possible to obtain such a sample and any screening programme may have to include the option of using "spot collections" taken at a single time point. Although "spot tests" are logistically less challenging than 24 hour samples, they have the disadvantage that they do not take into account the normal diurnal variations in urine production and metal excretion.

c. For analytical purposes, a large volume of urine is preferable since it allows greater concentration of the material of interest. A "spot test" however, does not necessarily imply a small (15 – 20ml) volume of urine, but may be the total volume of one or more voids over a period of time.

d. Comparison of 24 hour samples and "spot tests" has provided evidence for the utility of single time point collections in U analysis, albeit with a declining correlation between the two methods at lower U concentrations (<50ng/l)[8].

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[6] *Mirto, H., Henge-Napoli, M. H., Gilbert, R., Ansoborlo, E., Fournier, M. and Cambar, J. (1999), Intracellular behaviour of uranium(VI) on renal epithelial cell in culture (LL-PK1): Influence of uranium speciation, Toxicology Letters, **104**(3), 249-256.*

[7] *Rocskay, A. Z. and Robins, T. G. (1994), Assessment of a screening protocol for occupational renal disease, Journal of Occupational Medicine, **36**(10), 1100-1109.*

[8] *McDiarmid, M. A., Hooper, F. J., Squibb, K. and McPhaul, K. (1999), The utility of spot collection for urinary uranium determinations in depleted uranium exposed gulf war veterans, Health Physics, **77**(3), 261-264.*

e. Given the considerable difficulties involved in obtaining 24 hour samples, and the (limited) evidence to support single time point collections, it may be that "spot tests" (corrected for creatinine concentration) are employed as the sampling method of choice, provided a reasonable volume of urine can be collected at any one sampling point.

9. Analysis of urine – total U vs. isotopic ratio

a. As a primary screen for the assessment of DU exposure, the determination of total U in urine has been proposed. This technique is relatively straightforward and cost-effective. However, the lack of information on background U levels in a normal population means that only qualitative estimates can be made as to whether DU exposure has taken place. UK baseline levels of urinary U have been suggested of 10-35 ng/l although variations over 1 or 2 orders of magnitude are not uncommon due to regional variations and differences in dietary intake. The implementation of occupational screening (that is, comparison of total U levels in troops pre- and post-deployment) would allow a more meaningful comparison to be made, and provide reference data for a retrospective or population screening programme.

b. In order to demonstrate that exposure to DU has taken place, it is necessary to determine the ratio of U isotopes in urine. Natural U contains approximately 0.7% U^{235} and 99.2% U^{238}. DU however, being "man made", contains approximately 0.2% U^{235} and 99.7% U^{238} making it much less radioactive. Determination of DU exposure can therefore be carried out by analysing the ratio of U isotopes in the body.

c. Isotopic ratio analysis can be performed using fluorimetry or mass spectrometry (e.g. inductively coupled plasma mass spectrometry, ICPMS). In terms of sensitivity, mass spectrometry is the preferred technique, having a suggested limit of detection of around 10 ng total U per litre of urine, although a more realistic figure may be around 35 ng/l[9]. However, this is a relatively expensive technique and it may be that cost-effectiveness requires this analysis only in subjects where disproportionately high levels of total U have already been identified.

d. For *occupational* screening, one way of minimising unnecessary expenditure while still utilising the more sophisticated technique of mass spectrometry would be to collect and store a pre-deployment sample. This could then be analysed using mass spectroscopy at a later date only if the post-deployment sample gave any indication of variation in U isotopic ratio.

Analysis of bone

2. As a result of its ionic characteristics, UO_2^{2+} tends to compete with Ca^{2+} for certain transport mechanisms and is rapidly accumulated in bone[10]. Approximately 66% of the total body burden of U is estimated to reside in the skeleton[11,12,13], with clearance half lives being reported as 300-5000 days based on a two compartment pharmacokinetic model[14,15].

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[9] *Allain, P., Berre, S., Premel-Cabic, A., Mauras, Y., Delaporte, T. and Cournot, A. (1991), Investigation of the direct determination of uranium in plasma and urine by inductively coupled plasma mass spectroscopy, Analytica Chima Acta,* ***251****(1-2), 183-185.*

[10] *Arsenault, A. L. and Hunziker, E. B. (1988), Electron microscopic analysis of mineral deposits in the calcifying epiphyseal growth plate, Calcif. Tissue Int.,* ***42****, 119-126.*

[11] *International Commission on Radiological Protection (1979), Limits for intakes of radionuclides by workers, Pergamon Press, (ICRP publication 30).*

3. Since the skeleton represents a large, long-term depot for U accumulation it may provide an ideal site for analysis of retrospective total U exposure. Previously, techniques for bone analysis have been invasive and inconvenient, however, recent advances in the determination of trace metals in bone using *K x-ray fluorescence* have suggested a role for this technique in U analysis[16]. Since (for the purposes of a screening programme) the skeleton can be regarded as a "permanent" depot for accumulated DU, such an approach would be advantageous in that it is completely non-invasive. In addition, this method is far less likely to be influenced by normal physiological processes which may interfere with other proposed analytical procedures e.g. the influence of kidney function on U excretion.

4. Although this method of analysis is still relatively in its infancy, there is great potential in such an approach and, as far as the author is currently aware, work is being undertaken to improve the sensitivity and practical application of this analytical technique[17].

Analysis of hair

5. The use of hair analysis for the determination of exposure to environmental pollutants has received much (controversial) attention over the last few years. Whilst far from being a universal technique for biomonitoring, for many trace metals (including U) the analysis of hair using radiochemical neutron activated analysis has proved to be a reliable biological marker of occupational and environmental exposure[18,19]. There are however, many practical difficulties associated with hair analysis; not least the fact that military personnel tend to keep their hair very short, and cut at regular intervals thereby negating the value of this type of analysis in any retrospective screening programme.

6. Analytically, the processing of hair samples is fraught with difficulties. For example, there is likely to be more U on the surface of hair as a result of environmental contamination than there is contained within the keratin structure of the material. Such surface contamination would have to be removed before analysis – a process which is technically challenging and

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[12] *International Commission on Radiological Protection (1995), Age-dependent doses to members of the public from intake of radionuclides: Part 3, Ingestion dose coefficients, Pergamon Press, Oxford, (ICRP publication 69).*

[13] *International Commission on Radiological Protection (1996), Age-dependent doses to members of the public from intake of radionuclides: Part 4, Inhalation dose coefficients, Pergamon Press, Oxford, (ICRP publication 71).*

[14] *WHO (1998), Guidelines for drinking water quality, Addendum to volume 2, Health criteria and other supporting information, World Health Organisation.*

[15] *Kathren, R. L., McInroy, J. F., Moore, R. H. and Dietert, S. E. (1989), Uranium in the tissues of an occupationally exposed individual, Health Physics, **57**, 17-21.*

[16] *O'Meara, J. M., Chettle, D. R., McNeill, F. E. and Webber, C. E. (1997), The feasibility of measuring bone uranium concentrations in vivo using source excited K x-ray fluorescence, Physics in Medicine and Biology, **42**(6), 1109-1120.*

[17] *Personal communication: R. Shayer/D. Chettle, 22/01/01.*

[18] *Bencko, V. (1995), Use of human hair as a biomarker in the assessment of exposure to pollutants in occupational and environmental settings, Toxicology, **101**(1-2), 29-39.*

[19] *Byrne, A. R. and Benedik, L. (1991), Uranium content of blood, urine and hair of exposed and non-exposed persons determined by radiochemical neutron activation analysis with emphasis on quality control, Science of the Total Environment, **107**, 143-157.*

expensive (although some success has been reported using Na_2EDTA in the removal of trace metals from the hair surface[20]).

7. Given the technical difficulties associated with analysis of hair for U, and the large number of samples anticipated for such a study, the use of this method is not felt to be appropriate for the proposed screening protocol.

Analysis of blood

8. Blood analysis is often discounted in screening programmes due to its invasive nature, practical difficulties, and the associated distress to subjects as a result of sampling. It should be remembered, however, that there may be potential for useful information to be gained from the screening of specific markers of cell/DNA damage following known U exposure, and that analyses of validated biomarkers may provide reliable information for risk assessment and disease prevention[21].

9. Several studies have focused on the determination and characterisation of chromosome damage in circulating lymphocytes following exposure to U and other radioactive compounds[22,23]. Such studies may give an indication of the early biological effects of a compound or, in certain instances where "signature" damage (that is, specific aberrations known to be caused by a particular agent) is present, a definitive link between exposure and potential health risks. However, given the logistic considerations involved in blood sampling, this type of study is not felt to be appropriate for the proposed screening programme.

Analysis of faeces

10. Monitoring of U in faeces is recommended by the ICRP[2,3] for the assessment of exposure rapidly following ingestion. Since gastrointestinal absorption of U is poor (approximately 2 – 3% total ingested[24]) this metal is very quickly removed from the body and, as such, faecal analysis offers little relevance for a retrospective screening programme.

Whole body monitoring/Lung monitoring

11. Whole body monitoring is a useful technique to determine the lung burden soon after an acute intake of insoluble radionuclides (such as depleted uranium oxides) and is recommended by the ICRP[2,3] to assess exposure of industrial workers. However, its value as a primary screening procedure is limited.

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*[20] Raghupathy, L., Harada, M., Ohno, H., Naganuma, A., Imura, N. and Doi, R. (1988), Methods of removing external metal contamination from hair samples for environmental monitoring, Science of the Total Environment, **77**(2-3), 141-151.*

*[21] Au, W. W., McConnell, M. A., Wilkinson, G. S., Ramanujam, V. M. and Alcock, N. (1998), Population monitoring: experience with residents exposed to uranium mining/milling, Mutation Research, **405**(2), 237-245).*

*[22] Martin, F., Earl, R. and Tawn, E. J. (1991), A cytogenetic study of men occupationally exposed to uranium, Br. J. Ind. Med., **48**(2), 98-102.*

*[23] Kanda, R. (2000), Improvement of accuracy of chromosome aberration analysis for biological radiation dosimetry, J. Radiat. Res., **41**(1), 1-8.*

*[24] Wrenn, M., Durbin, P. and Willis, D. (1985), Metabolism of ingested uranium and radium, Health Physics, **48**, 601-633.*

12. There are only a handful of fixed monitors within the UK and some of these are not equipped with the germanium detectors which are necessary to record the very low levels of gamma radiation produced by depleted uranium. Furthermore, an individual screening procedure takes 20 -30 minutes to perform. It is not considered to a first line screening procedure but it may have value as a follow-up investigation should urinalysis suggest a raised intake of depleted uranium.

Calculation of DU exposure

13. Having established DU levels in the biological sample of choice (in this case, urine), estimates of exposure can be made through the use of sophisticated biokinetic models[2,3] although this is a complicated procedure and there are many variables to consider. These include the size of the intake, whether an exposure is acute or chronic, and the time between intake and assessment.

14. Exposure to DU becomes more difficult to detect as the size of the intake decreases and as the time between the exposure and the assessment increases. Even the most sophisticated tests will be unable to detect DU exposure if excretion of this material during the lag time between exposure and testing has reduced its concentration within the urine to below detectable levels.

15. Any assessment of urinary U will only give a "snapshot" of the U in the body at the time of sampling, and back-calculation of the results will not give sufficiently accurate results without the information on the duration and circumstances of exposure and how long ago exposure occurred. To obtain this information, sampling will need to be associated with a detailed questionnaire.

Choice of a reference value

16. One of the aims of the proposed screening programme is to explain the potential health effects of exposure to DU. By establishing urinary U and applying ICRP biokinetic models, an estimate of U intake can be made and a "body burden" compared to reference values of chemical toxicity or radiation dose in an attempt to quantify the risk to the individual.

17. An appropriate reference value for the upper limit of acceptable risk from ionising radiation could be the public annual dose limit of 1 milliSievert (mSv) as established by the Ionising Radiation Regulations 1999[22].

18. Given the extreme variation in known "background" or "normal" U levels in unexposed populations, it is very difficult to determine a similar reference value for the chemical toxicity of DU. If a clearer picture of normal U concentrations could be established, statistical interpretation of population U levels may allow certain "action levels" to be conceived below which the risk of DU toxicity is felt to be minimal.

SUMMARY AND DISCUSSION

19. While analysis of total U in urine would appear to be the most practicable approach for the proposed screening programme given the constraints of time, availability of accredited laboratories, potential numbers of samples, and cost involved, it is a technique that is not without its limitations.

20. The lack of reliable background data for "non-exposed" personnel will only allow qualitative conclusions to be drawn from the retrospective (*population*) screening, and total

[25] *Ionising Radiation Regulations 1999.*

urinary U is not a dependable indication of DU exposure. The introduction of *occupational* monitoring of total U in urine will greatly assist this, and any other, related assessment programmes. The determination of U isotopic ratio must be included in this analytical appraisal if a relationship between DU exposure and health effects is to be identified/discounted.

21. From an *occupational* screening perspective, this uncertainty of "normal" U levels in troops may be further confounded by the fact that personnel may already have completed tours to the Balkans or the Gulf. Therefore, their background U levels may already contain an element of DU and this data will be of no value in establishing "normal" reference values of U in service personnel. Troops may also find that they are involved in both screening programmes. To this end, "virgin" or non-exposed recruits would be required when developing a control database.

22. Ultimately, levels of U in urine will be a function of kidney performance, and this may in turn be influenced by the initial level and duration of U exposure. It is suggested therefore, that analytical techniques take into account kidney function by the monitoring of specific protein markers in individuals where elevated urinary U levels are observed.

U.S. SCREENING PROGRAMME

1. At the recent Conference on Illnesses amongst Gulf Veterans, Professor McDiarmid from the Department of Veteran Affairs Medical Centre in Baltimore presented details about the developing U.S. screening programme. The U.S. use 24-hour urine analysis, relating it to the amount of creatinine in the urine (gms). They believe both are necessary. The normal background uranium in urine range for the U.S. population is in the range 10-70ng/gm of creatinine. The upper limit for normal natural uranium is understood to be 600ng/l. In view of this the U.S. Department of Energy has set an action limit of 800ng U/per litre of urine as an investigation limit for uranium in urine although the occupational exposure limit is much higher (c2 orders of magnitude).

2. Since 1998 the U.S. military have offered voluntary assessment of urinary uranium. To date 287 samples have been analysed. A cut-off level of 50 ng is used. For readings above this, the sampling is repeated and if again found to be above the cut-off, then isotopic analysis is performed. To date only 12 samples have been reported as above the cut-off point and all are below 100ng. Analysis has shown that there is no difference in measurements between non exposed Servicemen on active duty and the potentially exposed Gulf Veterans. Furthermore, no relationship exists between urine levels and activity amongst the Gulf Veterans (e.g. inspection of damaged vehicles etc.).

3. Results of isotopic analysis are not yet available. The U.S. stresses that the interpretation of isotopic ratios is proving to be technically very difficult. There is no defined 'gold standard' by which to interpret whether DU exposure has/has not occurred. An Inter-laboratory comparison is presently underway but the basic tools/information required to identify exposure to discriminate depleted uranium exposure from natural background uranium at these low levels are not available yet. A US military laboratory at the Armed Forces Radiobiology Research Institute has developed a technique using inductively coupled mass spectrometry which has a much reduced sample preparation and analysis time. It is understood that this is being geared up to large scale use if necessary.

4. The US have stressed that what urinary uranium concentrations relate to the current body burden of uranium and not past exposure. Although if depleted uranium can be detected it may be possible to extrapolate back and estimate a past exposure this will be fraught with difficulty and inaccuracies. Also, the absence of detectable depleted uranium today will not rule out an individual having an exposure in the past.

5. The US can however compare the low levels of total urinary uranium obtained to date with the much higher occupational exposure levels. They also point out the relative high urinary levels in those veterans injured by DU shrapnel. This group has been closely followed up and there is no evidence of any health effects. Finally, they use the extensive studies of uranium miners to reassure people of the lack of any evidence of an excess of lung cancer or leukaemia related to uranium exposure.