

Draft 3

Item	Discussion and decisions	Action by
1	<p><u>Introduction</u></p> <p>a) The chairman opened the meeting by welcoming Wg Cdr John Aitken, who would now be attending as an observer from the Defence Medical Services Department in succession to Wg Cdr Charlie Wilcock.</p> <p>b) Mr Glennon announced that for personal reasons he was resigning his membership of the DUOB and would no longer be representing the National Gulf Veterans & Families Association. He thanked his fellow Board members and immediately withdrew. The chairman thanked Mr Glennon for his contributions.</p>	
2	<p><u>Minutes of last meeting</u></p> <p>a) Minor changes were agreed at the request of Professors Coggon and Hooper. Mr Brown expressed his feeling that the DUOB minutes generally tended to give undue prominence to minority views. He thought that although an accurate record of discussions, the minutes fail to reflect the balance of opinion in the wider scientific community. However, he did not propose any specific amendments to address this.</p> <p style="text-align: center;"><u>Action 14.1 Secretary to finalise and circulate minutes of the 13th DUOB</u></p> <p>b) Dr Paterson offered to obtain a copy of the recent Kuwaiti cancer registration data on behalf of the chairman.</p>	Secretary (completed 27.01.04)
3	<p><u>Matters arising from the last meeting</u></p> <p>i. <u>Draft advice on “negative” test results</u></p> <p>Professor Coggon said that he had not yet made the revisions. He felt that it was best to wait until results were available from the pilot exercises, when appropriate wording could be discussed by the full Board.</p> <p>ii. <u>List of potential participants for the pilot exercises</u></p> <p>The secretary reported that he had received a list of 69 names (resident in all parts of the UK and in Germany) from the Royal British Legion Gulf Veterans’ Branch. No names had yet been submitted by the NGV&FA. Dr Paterson said that he had deliberately not encouraged NGO staff to volunteer at this stage, although many of them would like to be tested for DU in due course.</p> <p>iii. <u>Health administration contractor</u></p> <p>The secretary said that an internet search and subsequent enquiries had yielded one potential contractor, which had expressed firm interest in tendering for the central co-ordinating role. The MoD contracts branch had sent the company a draft Statement of Requirement (SOR) for initial comment. Surg Cdre Baldock reported that he had been contacted by an employee of the company seeking general information about the DU testing programme. The chairman said that a choice of contractors was preferable, and therefore a search for other possible contractors should continue.</p> <p>iv. <u>Normative values study – use of catheters</u></p> <p>The chairman confirmed that he had written to the contractor on this point.</p> <p>v. <u>Normative values study – technical correspondence</u></p> <p>The secretary said that a copy of correspondence with the normative values contractor was available to be viewed at the meeting.</p> <p>vi. <u>Toxicity of tungsten</u></p> <p>Following correspondence with Dr Levy, the secretary had removed reference to tungsten from the DU basic fact sheet. Dr Levy confirmed that it was not appropriate to liken the toxicity of tungsten to that of mercury and lead.</p>	

Draft 3

	<p>vii. <u>Dates of Balkan operations</u></p> <p>The secretary reported that the relevant start date was August 5th 1994, when DU munitions were first used by US aircraft in Bosnia-Herzegovina.</p> <p>viii. <u>MoD policy for free-of-charge retrospective DU testing</u></p> <p>The secretary said that the retrospective DU test would be available free of charge to individuals who were:</p> <ul style="list-style-type: none"> • members of the UK armed forces on deployment; or • civilian employees of the UK Ministry of Defence; or • civilians working under contract to the UK Ministry of Defence; or • civilians employed by other UK Government departments or non-governmental organisations in support of UK military operations; <ul style="list-style-type: none"> • in the Persian Gulf area between August 1st 1990 and July 31st 1991; or • in the former Republic of Yugoslavia on or after August 5th 1994. <p>The MoD reserved the right to levy a charge for testing of individuals in other categories.</p>	
4	<p><u>Update on testing programme contracts</u></p> <p>i. <u>Laboratory analysis</u></p> <p>a) The chairman confirmed that contracts had now been awarded to two laboratories (<i>designated here "A" and "B"</i>), and that a meeting had been held with them on December 18th 2003 at which detailed arrangements were agreed.</p> <p>b) For the normative values study, Laboratory A was to be the initial recipient of all samples. It would take the volume of urine required for its own analysis and forward the balance to Laboratory B. All 24-hour samples were to be analysed at both laboratories. The labs were to discuss with the study contractor whether it was practical to aggregate pairs of spot samples into a standardised regime (say 4 per volunteer) in order to create sufficient volume for duplicate testing. If so, that would be done. If not, the two laboratories were each to analyse half the total number of spot samples.</p> <p><u>Action 14.2 Secretary to circulate the notes of the laboratories' meeting</u></p> <p>c) Professor Coggon said that the standardised sample containers agreed with the two laboratories were square-form HDPE bottles with secondary seal and forensic closure. A 2-litre bottle would be used for 24-hour samples and a 250 ml bottle for spot samples. An example of each was shown to the Board.</p> <p>d) Professor Hooper asked how quickly samples would be forwarded from Laboratory A: would this be on the day of receipt? Mr Brown said that would depend on the timing of appointments and sample delivery, as the labs tended to perform the analysis in batches. Professor Hooper was concerned about the risk of contamination when the bottles were opened at Laboratory A, and did not want them to remain there longer than necessary. Mr Brown said that the same procedures would apply as in the pilot studies.</p> <p>e) Dr Busby asked whether the spot and 24-hour samples would be from the same person. Professor Coggon said yes, and explained that comparisons were to be made between the results from spot and 24-hour samples; between those from successive spot samples, in order to explore diurnal variation; and between those from the single 24-hour sample and from a second (virtual) 24-hour sample made by combining all the individual spot results.</p> <p>f) Professor Spratt felt it would be challenging for the labs to get good data from small spot samples. The chairman said that exact details would be agreed with the normative study contractor. The general procedures were designed as far as practicable to allow the laboratories to be compared.</p> <p>g) Dr Busby said that unopened sample bottles from the same individual should be analysed by both labs. Professor Coggon said that the pilot testing of veterans would involve a 24-hour sample and a <u>single</u> spot sample from each participant. All 24-hour samples would be analysed by both laboratories (bottle received at A and forwarded to B), whilst the spot samples would be singly analysed, half of them by laboratory A and half by laboratory B.</p>	<p style="text-align: right;">Secretary (completed 02.02.04)</p>

Draft 3

samples would be singly analysed, half of them by laboratory A and half by laboratory B.

- h) Mr Brown commented that different spot samples from the same person can give significantly different results, and thus the laboratories cannot be properly compared in that way. The chairman said the comparison between laboratories would be based on the duplicate analysis of the 24-hour samples.
- i) Professor Hooper asked whether laboratory B would measure the creatinine content independently of laboratory A. Professor Coggon said it could, but only where necessary. Dr Busby said he thought the arrangements were open to fraud by laboratory A, which some of the veterans did not trust. Professor Coggon said the fact that some samples would go straight to laboratory B should provide reassurance. If odd results were obtained, the Board could investigate. Mr Brown said he felt that suspicions of laboratory A were inappropriate, and noted that lab B was content to work according to the planned arrangements.
- j) Dr Paterson recommended that all the creatinine measurements be carried out in the same laboratory. Dr Lewis said that the uranium analysis results too would be subject to variation, and an uncertainty budget was essential. He asked what arrangements were in place to review the quality control operated by the labs. The chairman replied that quality assurance was built into the SOR on which the awarded contracts were based. The duplicate testing would provide further assurance.
- k) Dr Lewis said this was not sufficient. The chairman noted that good agreement between the labs had been achieved in the pilot study. Furthermore it had always been the intention to include some duplicate testing in the main programme. Dr Lewis said the Board should demand control charts for both uranium and creatinine. He was not convinced that enough QC data would otherwise be available. The chairman felt that there would be sufficient samples in the pilot exercise to demonstrate the adequacy or otherwise of the laboratory analyses. However, he suggested that Dr Lewis should review the QA arrangements in the SOR for the laboratories and propose any additions that he thought necessary.

Action 14.3 Secretary to send the laboratories' SOR to Dr Lewis

Action 14.4 Dr Lewis to review the QA arrangements and prepare documentation for the Board on any enhancements he considered necessary

ii. Occupational Health (OH) departments

- a) Professor Coggon reported that he and the secretary had met with staff at the OH department at St. Thomas' hospital in London on December 19th. A Statement of Requirement had subsequently been drafted and agreed with both St. Thomas' and Glasgow Occupational Health, a division of the Glasgow Royal Infirmary. The secretary said that the MoD contracts branch had formally invited each hospital to tender for the clinical roles in the pilot exercises. Subject to satisfactory responses, it was hoped that contracts could be in place and effective from February 16th 2004.
- b) Professor Coggon said that the main action outstanding in respect of the pilot exercises was now to finalise the lists of test participants. The secretary reported that the provisional list for the London clinic currently contained only 14 names, twelve with addresses in the home counties (including Hampshire) and two of veterans living further north who had specifically asked to be seen in London. From the list of volunteers supplied by the RBL and those who had made direct contact with GVIU, there was a total of only four persons resident in Scotland. The provisional list for the Glasgow clinic had therefore been supplemented with the names of veterans in the northeast and northwest of England. The total so far was 26.
- c) Dr Paterson said that he knew of eight people who wished to be tested, and asked whether those should be added. The secretary said that a substantial number of individuals who had served in the police forensic service in Kosovo during 1999 also wanted to be checked for DU exposure. He had received a list of volunteers from that group and now had enough names in total to make up the nominal thirty for each clinic. However, it was for the Oversight Board to rule on the priority for allocating places in the pilot exercise. The chairman said that armed forces veterans should be included first, then any remaining places offered to the police.
- d) Dr Paterson asked how long it was likely to be before the main testing programme got

Secretary
(Done
02.02.04)
Dr Lewis

Draft 3

underway. The chairman said it would start as soon as the necessary lessons had been absorbed from the pilot exercises – in mid-2004. The secretary added that he had predicted May/June when responding to veterans' enquiries. Dr Paterson said he would contact the potential test candidates he knew and explain the position.

- e) The chairman said that draft instructions had been prepared on how to provide the 24-hour urine sample with minimal risk of contamination. The secretary explained that the initial draft had been based on a list of key points received from Laboratory A and designed for male participants only. The draft had subsequently been modified by the chairman and by Mr Brown, and was no longer gender-specific in its wording. The chairman read out the latest version.
- f) Professor Gilmore pointed out that there was no explicit direction to urinate directly into the sample bottle. Professor Coggon asked the secretary to reinstate earlier wording that had made this plain. A discussion ensued on the feasibility of the procedure for women. Dr Paterson said he would seek advice from colleagues in gynaecology who routinely requested 24-hour samples. Miss Wane said that in her opinion it should be possible for women to pass urine directly into the 2 litre bottle, provided that physical contact with the top of the bottle was permitted.
- g) Professor Coggon said that a separate version of the instructions should be prepared specifically for women, including provision for telephone contact with a female member of staff in GVIU if required. Participants should be asked when they attend the clinic if they had any problem in following the procedure. Professor Gilmore suggested stating that the bottle could be wiped down externally if needed. Dr Lewis added that a cloth that did not shed fibres should be specified. Mr Brown commented that no real difficulty had been encountered in the biological monitoring programme, despite the use of far smaller (100 ml) sample bottles.

Action 14.5 Secretary to produce and circulate to the DUOB separate versions of the urination instructions for men and women

- h) Professor Coggon outlined the procedure that had been agreed with the OH departments for operation of the pilot exercises. GVIU would write to each participant enclosing the factsheets, questionnaire, 2 litre sample bottle and urine collection instructions. Contact details would be passed to the relevant OH department, which would then write to offer an appointment at the clinic. The bottle was to be labelled with a serial number by writing directly onto it with a marker pen; no adhesive labels were to be used.
- i) Professor Coggon said that the handling of the questionnaire data must be decided upon. He suggested that it be entered on computer by GVIU. The test results received from the laboratories would be considered by the full DUOB and their interpretation agreed. Once that had been done, individuals could be notified by GVIU. The initial letter should make clear to participants that this process would inevitably mean a delay in getting their results. Anyone wishing to discuss the meaning of their test result could ask to speak by telephone with Dr Spittle.
- j) Dr Busby said that a copy of the completed questionnaire should be lodged with a third party. Dr Paterson said the pilot exercise procedures should be kept as much like those of the main programme as possible. He felt that data entry should be carried out at the chairman's department (the MRC Environmental Epidemiology Unit at Southampton General Hospital). The chairman confirmed that could be done. The method employed there was for two operators to enter the data independently, after which a comparison was made to check for errors. Dr Busby insisted that photocopying of the completed questionnaire, for the individual concerned if requested and for third party retention, be done as part of the pilot testing. The chairman agreed that it should be, since the pilot exercise would provide the only urinary DU test of the programme for those taking part.

iii. Healthcare administrator

- a) Professor Coggon reiterated that so far one healthcare company had expressed a positive interest in tendering for the central scheme administration (now excluding the clinical services). At least one other organisation should be identified if possible. An administrator would have to be in place by May/June 2004. He reported that a first draft of the application

Secretary
(completed
02.02.04)

Draft 3

form for the main programme had been prepared, and asked for it to be circulated to the Board for comment.

Action 14.6 Secretary to circulate the draft application form for comment

- b) Professor Coggon said that the reason for lodging copy questionnaires with an independent third party was to provide reassurance that the information could not be tampered with. If the individual participant agreed, their answers could be held by a solicitor and accessed if checking became necessary. However, any statistical analysis of the questionnaires should be carried out only through the Board. Professor Hooper said that the veterans he represented would want the copy information available to people of their choice. Professor Coggon stressed that it could not be made freely available for the purpose of statistical analysis.
- c) Dr Busby said the “third party” did not have to be independent, but rather someone whom the veterans trusted. He said that some people did not consider the DUOB fully independent. He claimed that veterans would want analysis carried out by the Board to be verified by someone like himself or Professor Hooper. It was not the intention to do research *per se*. The chairman said that raised questions over ethical approval. The DUOB was legally responsible for the information entrusted to it. A good case would be needed to justify access to the back-up copies.
- d) Dr Busby said that the copied information was meant to be “a pistol to the head” of the DUOB. He queried why it was felt necessary to seek each participant’s agreement. Several members of the Board responded that explicit consent was now a legal as well as an ethical requirement. Dr Busby said that the reason for the very existence of the Board was rooted in veterans’ perceptions, and asserted that its work would ultimately fail if they were not satisfied. Dr Paterson said the DUOB could not ignore the law. Informed consent was a complex issue. One must spell out at the start exactly what the purpose of holding any data was. Dr Busby said that in that case, the purpose should be explained on the questionnaire. He accepted that legal requirements must be met.
- e) Dr Levy said that he saw no problem in archiving a separate set of questionnaires for security. However, if some participants did not agree to this, the information would be incomplete. It was also not permissible to hold data for an unspecified future use. This last point was discussed by the Board at length.
- f) The chairman stated that any allegations of fraud would have to come before the DUOB. Dr Busby said that if, for example, all results reported by the Board were negative for DU, some of the veterans might be suspicious and wish to have the primary data re-examined. The chairman said that Dr Busby and Professor Hooper had no individual rights to the questionnaire answers, which would be entrusted to the Board as a whole. Dr Busby said that point was addressed by seeking the consent of the participants. Dr Paterson felt the Board ought to take legal advice.
- g) Professor Gilmore said that a distinction was to be drawn between primary data, which could be retained by a third party in case of any suspicion of fraud; and the database of aggregated findings, which must be controlled by the DUOB. The chairman said that anyone wishing to study the data would have to submit a protocol to the Board and obtain ethical approval. Dr Busby said it was not clear how the issue of a corrupted database would be handled.
- h) The chairman said that there had to be rules about access to the participants’ data. Professor Gilmore said the question was who could authorise reference to the copies. Dr Paterson asked whether the concerns would be addressed if the Board were to publish aggregated data at regular intervals. He stressed that ethical approval was essential for access to the primary data. Unrestricted viewing of it was simply not permitted by the law.
- i) The chairman said that individual participants were, of course, free to retain a copy of their own questionnaire. That would allow a check to be made of the original held by the Board without involving the third-party archive. If a discrepancy were found, a case would exist for reviewing all the retained questionnaires. Dr Paterson said that the third party would need authorisation from the Data Protection Agency in order to hold the information. Professor Coggon said that questionnaires could be checked if the individual participants gave their permission.

Secretary
(Done
02.02.04)

Draft 3

- j) The Board agreed that the questionnaires of test participants who ticked the relevant box would be copied and passed to a third party for retention. Professor Coggon said the laboratories would keep a record of the results they sent to the testing programme administrator, and that record would constitute a guard against fraud.
- k) Dr Lewis said that as all test measurements were effectively points within a range of possible true values, it was important to state uncertainties alongside the figures recorded in the central database. Professor Coggon was concerned that the error ranges quoted by the laboratories would not reflect the true measurement uncertainty. The guide to that was the interlaboratory comparison. Dr Lewis said he felt the Board was being insufficiently rigorous with the numerical data. The proper range of possible values must be quoted, since it would affect the interpretation of the result.
- l) Dr Levy said he thought Dr Lewis was making a valid point. Dr Lewis said that the issue was how much of the output data from the laboratories would go onto the database created by the administrator. Professor Coggon said the Board would decide the criteria by which the administrator would interpret the test results.
- m) Mr Brown said that the test uncertainty could not be based on the results of the pilot exercises. Dr Lewis said that for any kind of test measurement, enough runs must be carried out to establish the true measurement uncertainty before there was any inter-laboratory comparison. Such comparisons could not validate a method. Professor Coggon said that the labs had already conducted that exercise. The pilot study had shown that the difference between the results reported by different laboratories was greater than the quoted uncertainty ranges. Accuracy was more important than precision in this case. Dr Lewis said that precision was needed too. The point was discussed at length.
- n) Dr Lewis emphasised his view that sufficient laboratory data had to go into the database to allow the quality of the data to be judged. Dr Busby asked if there were a case for including spiked samples in the main programme. Dr Lewis said that was done routinely as part of the laboratory procedure. Professor Coggon said what mattered to a veteran was whether he or she had been exposed to DU, and if so, to how much. Since the original exposure was to be back-calculated using a pharmacokinetic model, it would be subject to other important sources of uncertainty in addition to the imprecision of the assay. The important thing was the range of possible starting doses. Dr Lewis said that range ultimately depended on the initial measurement. Professor Coggon replied that nonetheless the precision of that measurement was not necessarily the critical determinant, since there could be much larger errors from other sources.
- o) Dr Spittle said that her main concern was the uncertainty around zero: that is, whether DU had been found or not. Professor Coggon said it had been decided that an atomic ratio [$^{238}\text{U}/^{235}\text{U}$] above a threshold of 142 could be interpreted as evidence of DU. Dr Lewis said that was based on the pilot study findings, and the standard of performance by the laboratories might not be the same in the main programme. Dr Busby asked if the Board could not simply include externally spiked samples. Professor Coggon said that this was planned as part of the main testing programme, but that to do so in the pilot testing would mean additional contracting and delays. It was important to press ahead with the launch of the testing programme. He asked that Dr Lewis review the technical requirements of the existing laboratory contracts and document for the Board anything further that he felt should be done, specifying exactly how the uncertainty range might be calculated.

Action 14.7 Dr Lewis to review the laboratory contracts and advise on further uncertainty estimation

iv. Normative values study

The chairman said that a contract was in place for the preliminary (25 person) phase of the civilian normative values study. The work was nominally underway, although no progress reports had yet been received from the contractor.

[Post-meeting note: The duration of the study as envisaged in the contract is January 2nd – September 30th 2004]

Action 14.8 Secretary to circulate the study protocol to the Board

Dr Lewis

Secretary
(Done
02.02.04)

Draft 3

	<p>and it was hoped that all participants could be seen in the six week period from then to the end of March. Results could be expected from the laboratories about a month later. There would then have to be a lengthy meeting of the DUOB to consider their interpretation. The secretary said that a Statement of Requirements for the healthcare administration role had been drafted, but could not be finalised until after the pilot exercises. Therefore a contract for main programme administration would not be possible until May or June.</p>	
8	<p><u>DU background and scientific issues</u></p> <p>i. <u>Paper by Gwiazda <i>et al</i> on urinary uranium assay</u></p> <p>Professor Spratt said there was no attempt in the paper to convert the urinary uranium concentration measurements into levels of exposure. He felt it was interesting that an artefact from the direct injection of urine into the spectrometer had led to the impression of enriched uranium. Dr Lewis said it was surprising that the researchers had not diluted the samples. Professor Coggon noted that the DUOB assay had higher sensitivity. Professor Spratt suggested that Dr Etherington be asked to comment on the significance of the two high results.</p> <p>ii. <u>Other papers</u></p> <p>a) Professor Coggon mentioned “Mortality among a cohort of uranium mill workers” (Occ. Environ. Med. 2004: 61: 57-64), which had reported on a number of cancers. Members of the Board expressed an interest in seeing the paper.</p> <p><u>Action 14.12 Secretary to download the paper and circulate hard copies to the Board</u></p> <p>b) Professor Coggon noted that various other papers had been circulated since the last meeting. Professor Hooper drew the Board’s attention to the material he had contributed on birth defects. Dr Busby referred to a report on leukaemia and birth defects in Iraq since 1990 that he had seen at a recent conference in Hamburg. He advised caution in interpreting the data, noting that the absolute incidence of these conditions in Iraq was only now approaching the levels seen in the UK and western world in general. Although there had been a rapid rise in incidence rates, they were still not high. Possible explanations were better reporting and the generally lower cancer rates in less developed, and less polluted, areas. Dr Spittle said that life expectancy is also greater in the west, leading to more opportunity for cancer to develop. Dr Busby said the figures were standardised for age, and cancer was increasing even among the young.</p> <p>c) Professor Spratt enquired about the Doyle study of reproductive health. Professor Coggon said it was in press.</p>	Secretary
9	<p><u>Dates of next meetings</u></p> <p>The chairman said that the date chosen for the next DUOB meeting, March 23rd, should be considered provisional. It would become clear nearer the time whether the Board needed to convene in March. Meanwhile he asked the secretary to canvass the availability of members for a meeting in May.</p> <p><u>Action 14.13 Secretary to canvass members for available dates in May</u></p>	Secretary (Done 02.02.04)
10	<p><u>Any other business</u></p> <p>Professor Hooper asked the secretary for information about the potential healthcare administration contractor.</p> <p><u>Action 14.14 Secretary to send contractor information to Professor Hooper</u></p>	Secretary (Done 02.02.04)

Distribution:

All members

All observers