Terms of reference

1. To review the published and emerging scientific findings of the UK MRC/MoD Gulf veterans’ illnesses research programme in the context of international Gulf veterans’ illnesses research.

2. To advise the MRC on the main scientific conclusions from the MRC/MoD Gulf veterans’ illnesses research programme in the context of other UK and overseas military health research.

3. Taking into account the need for scientific quality and value-for-money in an international context, to identify any gaps or areas where UK follow-up studies or other research may be feasible and worthwhile; or whether no further research is required.

4. To advise whether there are any other steps that MoD could take to facilitate MRC/MoD Gulf veterans’ illnesses research.
Background

1990 - 1991  Around 53,000 UK services personnel were deployed to the Persian Gulf as part of the coalition forces sent there in response to Iraq’s invasion of Kuwait. Many were directly involved in the resulting conflict and subsequent operations.

1991 - present  A proportion of Gulf veterans (GVs) from several of the coalition countries that took part in the conflict report suffering from ill health. Their complaints cover a wide range of ailments that is broadly similar between countries. No definitive cause has been identified, but exposures to chemical, biological or radiological hazards, and pre-emptive chemical and biological weapons treatments, have been suggested as possible contributory factors.

March 1996  The Medical Research Council (MRC) advised the Ministry of Defence (MoD) that an independent research programme was needed to look into UK GVs’ illnesses. As a result, MRC invited research plans aimed at finding out:

i. whether UK GVs were more ill than they would have been if they had not served in the Gulf and if so, what, and how much more, illness did they suffer;

ii. whether Gulf deployment adversely affected pregnancies and/or children later conceived by UK GVs and, if effects were found, what were they and how much more often did they happen than in non-GVs.

1997 - 2002  Several studies, of different durations, which had been reviewed and recommended by the MRC, were funded by the MoD to address these research questions.

An MRC Gulf War Illness Steering Committee (GWISC - originally the Gulf War Illness Scientific Advisory Committee), independently monitored UK research projects, kept abreast of GVs’ illnesses research and advised on the programme’s strategic direction. GWISC gave independent scientific advice to the MoD via a Gulf War Illness Research Liaison Committee. This was set up to provide an interface between MRC/MoD experts and research grant applicants, to help to co-ordinate research projects, and to consider how best to manage the data collected so that it could be used in further research.

Autumn 2000  The UK studies’ preliminary findings suggested that there was no evidence of a unique Gulf conflict related syndrome, or an increased death rate among GVs. Post-traumatic stress disorder could account for some of the reported symptoms, but it could not explain most of them. MRC advice was that the Gulf conflict gave rise to important lessons, particularly regarding record keeping, preventative medicine, recognition of risks and dealing with traumatic stress. MRC advised the MoD’s Chief Scientific Adviser that it would not be appropriate to begin any new Gulf health research initiatives, other than long-term monitoring of GVs’ health, until the results of ongoing studies were known.

June 2001  MRC set up a Military Health Research Advisory Group (MHRAG, membership listed opposite) to replace the GWISC, maintain expertise in the area, and be ready to give Government independent scientific advice if necessary.

July 2002  MRC decided to carry out an independent review of research related to GVs’ illnesses following an MoD request for advice. The review’s terms of reference are listed opposite.

January 2003  MHRAG conducted this review. They first held a meeting of scientists from the UK and overseas representatives to get an up-to-the moment perspective of UK GVs’ illnesses research, to hear about what other countries are doing, and to gather expert views from scientists outside the field. MHRAG then met separately to appraise the MRC of scientific progress, of the potential for gaining further knowledge and of research needs, and of what the likely medical issues might be. This report summarises the scientific findings and conclusions of these meetings.
Gulf veterans' illnesses research: UK findings

Epidemiological studies

Epidemiological studies compared data from random samples of Gulf veterans (GVs) and military contemporaries with equivalent age, gender, officer status, and service-arm profiles, who had served elsewhere (non-GV). A retrospective study of cancer and death rates gathered data on nearly all of the 53,000 UK GVs. Studies of ill health and reproductive health, and a three-stage follow-up study of GVs' health over time, surveyed thousands of GVs and non-GVs. They completed questionnaires about their current health and their recall of exposure to potential health hazards. Epidemiologists also reviewed over 400 published studies which had compared ill GVs with non-Gulf controls to investigate possible links between Gulf deployment and ill health.

General health

- In general, military populations are healthier than civilians; this is called the 'healthy warrior' effect. UK and international statistics show that GVs' death rates from all causes, including cancer and suicide, are not significantly higher than in non-GVs. UK and US GVs have had slightly more accidents, for example road traffic accidents, than non-GVs. This might be due to increased risk-taking activity.

- Over a decade after deployment in the 1991 Gulf conflict, some GVs still suffer ill health. However, there is no unique Gulf War Syndrome. The same symptoms and symptom groupings are also seen to some extent in all non-GV control groups. The only common Gulf conflict related experience seems to involve ill GVs' perception of their health.

- Around twice as many GVs as non-GVs (24% vs 10%) consistently reported having more of the different symptoms they were asked about and suffering more severely from them. Common complaints included tiredness, headaches, lack of concentration, memory loss and numbness, tingling, or weakness in the arms and legs.

- Thorough medical examinations and physical, psychological and psychiatric testing of ill GVs detected no obvious major abnormalities. Minor differences found in some tests (see following) were not enough to account for the scale of illness seen.

- GVs' reported health problems are worse the lower their rank is, and after they have left the forces. Some studies found that UK GVs who report more severe symptoms are more likely to recall having had more inoculations at the time, and remember handling pesticides more often. However, UK GVs' perception of their current health is known to influence their recall of original hazards and exposures. GVs from countries that did not use the same vaccinations or anti-nerve gas agents also report similar symptoms.

- In contrast to non-GV control groups, ill GVs report more of every hazard and exposure they might have encountered, and recall exposure to more of these over time, while those in good health remember fewer exposures. Some hazards are recalled more reliably than others. GVs' recollections of oil fires and scud missile alarms are reasonably consistent, but there is less certainty about exposure to pesticides and chemicals, and even less reliable information about possible contact with depleted uranium.

Epidemiology

Epidemiology looks at the patterns and distribution of disease in different groups of people, to find out what its causes are and identify factors that make some people more susceptible than others.

The MRC/MoD Gulf veterans' illnesses research programme funded several epidemiological studies. These set out first to look for common factors specific to Gulf service that might explain GVs' illnesses, so that any promising leads could then be further investigated to pin down the causes.

Independent records or measurements, showing precisely what people were exposed to, produce the strongest epidemiological evidence. A dearth of such details about the 1991 Gulf conflict has consistently impeded later epidemiological studies. For this reason, most research has had to rely on GV's recollections, often more than five years after their Gulf service.
Reproductive health

Reproductive health studies asked men and women who conceived or attempted to conceive after the Gulf conflict about their fertility, about failed pregnancies and birth defects, and about their children’s health. When interpreting the results of such studies, it is important to consider possible reporting and self-selection biases.

- An analysis of self-reported miscarriages, stillbirths and malformations according to parental Gulf conflict status and specific exposures has been submitted for publication and analysis of infertility and children’s health is ongoing.

- Although two out of four reproductive health studies reviewed showed an increased incidence of self-reported birth defects among GVs, their independent measures of birth defects found no association with Gulf service or reported exposure to particular hazards. Such studies have identified no clear patterns of well-defined abnormalities.

Organophosphates

Organophosphates (OPs) are a family of chemicals that affect nerve signal transmission by a molecule called N-acetylcholine, which operates throughout the nervous system in many species. OPs have toxic effects that are due largely to their capacity to bind to and inhibit the enzyme acetylcholinesterase (ACE), which breaks down acetylcholine. This causes a build-up of N-acetylcholine at nerve junctions that disrupts widespread physiological processes. Different OPs inhibit ACE and related enzymes to very different extents. OPs that block insect ACEs but have less effect in humans are used in pesticides, for example sheep dip. Those that affect humans have medical applications, but have also been developed as nerve gasses, for example sarin. OP pesticides and nerve gasses were both potential hazards in the 1991 Gulf conflict.

The immediate effects of OP poisoning are headaches, diarrhoea and paralysis. Some, but not all, OPs may also cause delayed nerve damage, leading to muscle weakness that begins up to two weeks after exposure and lasts one or two weeks (intermediate syndrome). However, this is not related to their ability to inhibit ACE. Little is known about how OPs affect other biological processes, or the effects of low-level OP exposure. A 2003 Department of Health report on OPs (www.doh.gov.uk/com/com.htm) describes subtle effects that linger after acute poisoning, eg, with sheep dip, but no evidence for these effects with low-level exposures. Reported OP-induced bone formation defects in animals and long-term neuropsychiatric illness in people have not been verified.

The evidence linking UK GVs’ illnesses to actual measures of nerve gas or OP pesticide exposure is extremely poor. There is no confirmed evidence that nerve gasses were used in the 1991 Gulf conflict. OP pesticides used by troops stationed in the Gulf were the only likely OP hazard. However, there is little information on the quantity of OP pesticides people handled, or how these were used. No cases of acute OP poisoning were reported at the time, making it unlikely that exposure levels were ever high enough to account for the kinds of symptoms experienced later. The US Institute of Medicine published a review of studies relating to use of OPs and pesticides in the Gulf (www.nap.edu/books/030908458X/html/) in February 2003. Suggestions of a weak epidemiological link between ill health and self-reported OP exposure are difficult to interpret, especially because health status is known to influence exposure recall over time. However, it is possible that some people are particularly sensitive to certain OPs due to naturally occurring genetic differences in the enzymes that break down OPs. UK and US studies have found reduced activity of one such enzyme - paraoxonase 1 (PON1) - in some ill GVs and in some farmers affected by OP sheep dip. The significance of these findings is not yet clear. PON1 breaks down different OPs at different rates and has a number of other functions that relate to common health problems, eg, cardiovascular disease. Furthermore, the natural variation of PON1 activity in the general population is not known. Studies of how PON1 activity relates to genetic make-up, of whether it varies over time, and of whether it relates to GV’s illnesses in people not exposed to OPs might help to resolve these questions.
Clinical investigations

Some ill GVs from the first-stage of the follow-up study were examined further. After a general health assessment, they underwent an extensive battery of physical, biochemical and behavioural tests. These included detailed investigations of nerve, muscle and immune system function, thinking, behaviour and mental health. Blood samples were stored for further analysis.

Immunology and genetics

- There is little evidence that vaccination was a cause of GVs’ illnesses. One study tentatively linked self-reported symptoms to vaccinations and another found that ill GVs had differences in some immune system measurements. However, the significance of these findings is unclear. No commonly accepted mechanism could account for immune system related symptoms persisting more than 10 years after vaccination.
- Epidemiological data from a study based on replies to questions about vaccination records suggested that ill health - in particular skin and musculoskeletal problems - might relate to the number of pre-emptive anti-chemical and biological weapon vaccinations received in the Gulf. However, recall of vaccinations is not always consistent with the patchy records that exist. In general, reports of long-term effects from multiple vaccinations do not tally with a lack of atypical side-effects reported immediately after vaccination.
- Levels of the enzyme paraoxonase 1 (PON1 - see Organophosphates p4) were lower overall in GVs than non-GVs, and particularly low in ill GVs. However, the pattern of different PON1 gene variants was not associated with Gulf deployment or ill health.
- One study found evidence of a shift in the balance between two groups of immune system signalling molecules - Th1 and Th2 cytokines - in favour of Th2, and evidence of a weaker immune response in blood from ill GVs compared to non-GV controls. However, it is not certain whether variations in Th1/Th2 levels of the sizes measured are anything unusual. They could be caused by recent vaccinations, stress, or other factors, but no commonly accepted mechanism can explain how such differences could persist 10 years after vaccinations given in 1991.

Neurology

- Although ill GVs consistently report an unusually high level of neurological symptoms, clinical investigations detected no substantive evidence of malfunction in the peripheral nervous system, or nerve/muscle junctions.
- Slightly worse muscle strength and endurance found in some people may have been due to changes in lifestyle after leaving the services, or some unknown biological factor.
- These symptoms do not fit the expected pattern for damage to peripheral nerves or nerve/muscle junctions caused by exposure to organophosphates.

Neuropsychology

Problems with memory, concentration and mood disturbances are among the most common symptoms that ill GVs report. However, international research in the area is limited. Only a few studies have been carried out, and some used small and self-selected GV samples and poor controls. A better controlled and designed UK study has provided more robust findings. Neuropsychological tests measured parameters such as general attention, motor skills, memory and recognition, and cognitive function questionnaires assessed how clearly people think and how well they react to mental challenges.

- As with all other symptoms, ill GVs report more and worse symptoms of depression, anxiety, and mental impairment. They report mood disorders more often than cognitive difficulties. Depression increases the number of symptoms a person reports.
- Minor subjective and objective cognitive impairments are fairly common. However, tests do not identify any major neuropsychological problems and there is no correlation between how badly people think their concentration and memory are affected and how well they do in objective tests of mental function.
Chemical and biological weapon precautions

Most UK armed service personnel deployed to the Gulf were vaccinated and also received nerve agent pre-treatment tablets as a precaution against possible attack by chemical and biological weapons.

Nerve agent pretreatments

Nerve agent pre-treatment tablets (NAPS) protect people against attack by organophosphate-based nerve agents. The active ingredient in NAPS is a compound called Pyridostigmine Bromide (PB), which modifies acetylcholinesterase (ACE) to prevent it from reacting with OPs (see Organophosphates, p4, for explanation of OP toxicity).

The effects of PB in animals and human volunteers are well known and typical of anti-ACE agents; they include wheezing, vision disturbances, diarrhoea and sweating. PB is routinely used to treat myasthenia gravis, a disease of nerve/muscle junctions. Recommended doses can be much higher than those in NAPS and are generally administered for much longer. However, PB’s effects in combination with other chemicals, eg insecticides and insect repellents, or with vaccines, genetics or stress, are not known and are difficult to study.

An MoD study of possible interactions between PB and different vaccine combinations (see Vaccinations) in primates is underway. The study will mirror human doses, to measure both the physiological and the behavioural effects of multiple vaccinations with and without PB, and the long-term effects of low-dose nerve agents. Results are expected at the end of 2003.

Vaccinations

In addition to the usual immunisations for people travelling to the region, most UK armed service personnel deployed to the Gulf were also inoculated in case of biological attack by plague, and anthrax. Whooping cough (pertussis) vaccine was used to boost the immune response. Different vaccines were given in combined doses according to conventional medical procedures. Other countries, whose GVs report similar ill health symptoms, used different vaccine combinations and vaccination schedules. The US, for example, did not use plague or pertussis, but did use botulism, and French and some Canadian troops were not vaccinated at all.

Some UK epidemiologists found an association between the number and severity of recorded symptoms and the number of vaccinations received in the Gulf. However, the significance of this link is unclear because Gulf vaccination records are incomplete and health status is known to affect self-reported hazard exposure over time.

Psychiatry

- Objective impairments could be caused by anxiety or depression, which may or may not relate to previous exposure to nerve damaging agents. If depressed people expect to do worse in tests, or feel that they are doing worse than they actually are during testing and react badly when they make minor errors, their performance may deteriorate.

- According to estimates based on the samples analysed, three-quarters of ill GVs have no recognised psychiatric disorder.

- In total, GVs report more psychiatric symptoms, and symptoms of greater severity than non-GVs, but not enough to account for the observed excess of ill health. Among all GVs, Gulf service increases the overall risk of symptoms by up to three times, but there are considerable differences between studies.

- GVs do have an increased risk of post-traumatic stress disorder, but it only affects around three per cent of them, which is not enough to explain all GVs’ illnesses. Depression and alcohol are much more important health risk factors.
Long-term health

- On the whole, ill GVs are gradually getting better, but they are still in significantly worse health than non-GVs.
- Those who have left the forces have more symptoms of post-traumatic stress disorder and worse mental health than those still in service. People with these problems are more likely to leave the forces and to have trouble finding employment.
- Although GVs are more likely to suffer ill health, those who remain well have greater than average chances of finding work after leaving the forces.

Sociological and historical research

Several studies have sought the opinions of both sick and well GVs. Although many believe that their service adversely affected their health, there remains considerable loyalty to the UK Armed Forces. As with many other conflicts, some veterans don’t cope well with reintegration into civilian life and are left disillusioned, disaffected and unhappy. Some see their predicament as a general cost of life in the services, while others attribute ill health specifically to service in the Gulf and the hazards they encountered there.

GVs’ illnesses are one of the most recent examples of post-combat health problems that have been recorded since the Crimean War (1854-56). Although such conditions have been associated with all the major conflicts of the 20th century, little is understood about their precise causes. One theory is that they are triggered by the physical and psychological adversity common to all conflicts and that the pattern of illness is determined by veterans’ experiences both during and after wars. In the past symptoms included localised sensations of pain or numbness, chronic fatigue, fainting, and anxiety; whereas today neuropsychiatric symptoms are more common. It is possible that post-combat illnesses with similar causes are moulded into different forms by the prevailing technologies, health concerns and cultural attitudes of different eras.

Depleted uranium

Depleted uranium (DU) is a reduced radioactivity by-product of uranium enrichment processing by the nuclear industry. Its high density - almost twice that of lead - is exploited for military uses in armour plating and tank-busting ammunition. Like other heavy metals, for example lead and mercury, DU is a chemical toxin. It is also mildly radioactive (ie, relatively low specific activity), emitting alpha particles which do not have enough energy to penetrate human skin but can damage cells and molecules if inhaled or ingested.

Armour-piercing munitions contain DU rods that punch through heavy armour on impact, producing damaging shrapnel inside the vehicle and a cloud of fine DU particles that burns spontaneously in air to form uranium oxide. In the 1991 Gulf conflict, DU shrapnel wounds and uranium oxide dust inhaled in vehicles when, or shortly after they were hit by DU rounds, were potential sources of DU exposure.

Although animal studies indicate that sufficiently large short-term doses of uranium can cause kidney damage, the very limited human data available from uranium miners and accidental exposures, suggest that the risk of acute poisoning in humans is not great. Very little is known of the effects of long-term exposure to low levels of uranium. A Royal Society report, The health effects of depleted uranium munitions Part II, which was published in March 2002 (www.royalsoc.ac.uk/files/statfiles/document-168.pdf), concluded that, injuries aside, the chemical and radiological risks DU munitions pose to soldiers are very low. The civilian UK population is exposed to alpha radiation in the natural environment, for example from radon gas, at levels that are likely to be greater than from modest DU exposures.

The nature and extent of DU exposure in UK troops is not known. The MoD is conducting a DU research programme, and has funded the development of a urine test for the presence of DU. Work on the test has been overseen by an independent board which includes leading UK scientists. If the pilot study shows that the test is sensitive enough to verify DU exposures that may have occurred in the Gulf conflict, GVs will be offered retrospective screening to assess their DU exposure. Epidemiological studies to investigate the relationship between ill health and DU levels in urine are also planned.
Conclusions and recommendations

The international perspective

The UK GVs’ illnesses research programme is very highly regarded internationally. Everybody at the meeting agreed that the UK studies were well-focussed, high-quality, and have provided excellent value for money. They have influenced the international approach to GVs’ illnesses research and made a critical contribution to international understanding.

The UK programme’s findings broadly agree with those of international research, including much more extensive US studies. There is a notably similar pattern of findings irrespective of where GVs came from, or what their Gulf service experiences were. GVs from several coalition countries consistently report suffering from more symptoms than non-GVs, and these symptoms are similar despite markedly different exposures to vaccination, nerve agent pre-treatments, oil fire smoke and other potential hazards. Increasingly detailed medical investigations have detected very few actual abnormalities and no consistent associations. In short, there is no evidence from UK or international research for a single syndrome related specifically to service in the Gulf.

Research studies everywhere had been hampered by a lack of baseline exposure data on which to base trends, and by the difficulty of retrospectively verifying self-reported exposure data, which are sensitive to bias, and vary and become less reliable over time.

Areas where no new work is needed

Further studies to characterise symptoms and illnesses of UK GVs based on self-reported exposures are not necessary and epidemiological studies of existing data are unlikely to lead to greater understanding.

Most of the potential hazards have already been investigated in sufficient detail.

- There is no scientific need for more studies of DU effects in UK GVs other than the work already planned as part of the MoD’s DU research programme. There is a large ongoing research programme in the US. The UK Royal Society working group has already published two comprehensive reports.

- The Department for Environment, Food and Rural Affairs, the Department of Health, and the Health and Safety Executive are jointly funding several research projects investigating the long-term effects of OP insecticide exposure.

- The lack of substantiated vaccine exposure data means it is unlikely that existing study groups will yield any more useful information.

- Yet-to-be published reproductive health findings will determine whether further research in that area is needed.
### Conclusions and recommendations (continued)

#### Further research
- Research aimed at improving the long-term health of GVs with persistent symptoms should take priority. Information about people’s long-term health will contribute to improved interventions. Cognitive, behavioural and social follow-up studies are recommended, as greater understanding of how people cope with ill health is likely to lead to better models for psychological treatment of military personnel and others.

- Collection of follow-up data on GVs’ children should be considered, depending on the as yet unpublished results of ongoing reproductive health studies.

- Gathering cancer and death statistics from NHS data is cost-effective and should continue. Linking this data to exposure data from epidemiological studies might provide useful information at little extra cost.

- The possibility of paraoxonase enzyme genotype studies should be explored. Comparing non-exposed and exposed individuals, with or without symptoms, might show whether symptom severity correlates with particular enzyme subtypes.

- There should be a review of GVs’ symptoms related to the vaccine schedules used by different coalition countries in the 1991 Gulf conflict. Research findings on vaccination in the general population should be monitored as they may shed light on vaccine effects in military populations. Pilot work would be needed to gauge the feasibility of any future clinical trial investigating anti-biological warfare vaccines used in troops, either singly or in combination.

- Preliminary US neuroimaging studies should be replicated in the UK. Studies of measurable symptoms should be piloted to see whether nervous system changes are also present. The cognitive functions/malfunctions sustaining perceptions of illness should be robustly and rigorously investigated. Such studies could involve either GVs, or another military population with comparable symptoms.

#### Other advice to the MoD
- Research into the factors affecting the reintegration of discharged troops and reservists into civilian life would be worthwhile, to help to minimise problems associated with this transition.

- Lack of baseline data impeded UK GVs’ illnesses research. Canada and the US are starting to collect data on the current health status and previous exposures of new recruits, and plan to update these records throughout recruits’ military careers. They are also looking at ways to monitor exposures in the field. Setting up similar systems in the UK would improve the quality and ease of future military health research.

- The MoD should consider the ethics and feasibility of routinely linking forces’ data with national medical data, which would greatly help future research.