The challenges of exposure assessment in health studies of Gulf War veterans

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A variety of exposures have been investigated in Gulf War veterans' health studies. These have most commonly been by self-report in a postal questionnaire but modelling and bio-monitoring have also been employed. Exposure assessment is difficult to do well in studies of any workplace environment. It is made more difficult in Gulf War studies where there are a number and variety of possible exposures, no agreed metrics for individual exposures and few contemporary records associating the exposure with an individual. In some studies, the exposure assessment was carried out some years after the war and in the context of media interest. Several studies have examined different ways to test the accuracy of exposure reporting in Gulf War cohorts. There is some evidence from Gulf War studies that self-reported exposures were subject to recall bias but it is difficult to assess the extent. Occupational exposure-assessment methodology can provide insights into the exposure-assessment process and how to do it well. This is discussed in the context of the Gulf War studies. Alternative exposure-assessment methodologies are presented, although these may not be suitable for widespread use in veteran studies. Due to the poor quality of and accessibility of objective military exposure records, self-assessed exposure questionnaires are likely to remain the main instrument for assessing the exposure for a large number of veterans. If this is to be the case, then validation methods with more objective methods need to be included in future study designs.

Keywords: Gulf war veterans; exposure; chemical warfare; uranium

1. INTRODUCTION

Over the past 15 years, a very large Gulf War literature has accumulated. Gulf War epidemiological research has often compared a wide range of health outcomes in Gulf War veterans with health outcomes in military comparison groups.

Service in the Gulf has been a common exposure metric in these studies, and this should be a straightforward exposure variable to measure accurately. In practice, this has not always proved to be the case, as nominal rolls of Gulf War veterans have been found to be inaccurate. For example, 8.5% of a sample in a US Department of Defense database never actually deployed (McCauley *et al.* 1999). Thus, such an apparently straightforward method as the use of nominal rolls to assess Gulf War service (as the measure of 'yes' or 'no' regarding Gulf War exposure) can introduce significant exposure measurement error. In studies where subjects are in contact, much of this error should be detected and corrected, but this can be a major problem in linkage studies, e.g. studies where subjects are not in individual contact.

Measurement of specific Gulf War and other war exposures, especially retrospectively, is considerably more difficult than the use of the 'Gulf War service' metric. In the Gulf War literature, most of the studies have had considerably more complex exposure metrics

relating to specific exposures related to Gulf War service, such as pesticide or depleted uranium (DU) exposure, and these methods can involve considerably greater challenges to avoid exposure measurement error. Detecting and preventing ill health arising from war deployment in the future will require the identification of valid associations between the specific war exposure(s) and ill health and the implications of such findings to modify battlefield exposures in the future.

In thinking about how the Gulf War exposures have been measured in the Gulf War literature, and the ways that this can be improved in the future, there is much that we can learn from the discipline of occupational epidemiology. In the past couple of decades, occupational exposure assessment has developed to assess more validly and reproducibly the exposures encountered in a person's workplace, such as the Gulf War theatre.

In this paper, we review the exposure-assessment methods which have been used in the Gulf War epidemiological literature to date, identify the weaknesses and limitations in such methods and suggest measures to improve exposure assessment in future studies of health effects from specific Gulf War exposures. We have restricted considerations of exposure assessment to environmental, chemical, physical and biological exposures, and have largely excluded psychological exposures or stressors and medical interventions such as vaccinations or provision of pyridostigmine bromide (PB), but these considerations apply equally to these types of exposures as well.

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2. WHY IS EXPOSURE ASSESSMENT IMPORTANT?

There are several reasons why we should be concerned by not being able to identify and measure exposures in a deployed area, such as the Gulf War, in addition to research purposes. Firstly, there are immediate operational reasons to help minimize or reduce disease and battle and non-battle injuries which may result in decreased mission performance (Hauschild 2000). Secondly, there is evidence that, following deployment, the most symptomatic members of the military are most likely to leave (Hotopf & Wessely 2005), so if exposure(s) cause symptoms, a Defence Force will lose trained and experienced members. Last but not least, a Defence Force has a duty of care to, as far as possible, look after the health of its members, including the quality of life during and after deployment. Therefore, we need methods to take risk-management decisions in the field, which requires the identification and measurement of significant exposures. Wherever possible, such exposure assessment should also be useful to develop exposure metrics for later research purposes. If an exposure which causes ill health is not accurately identified and measured for later research, any association and causal link may not be identified, especially if the association is only of weak to moderate strength.

Assessment of infectious agent exposure, leading to improvements in vector control or improvements in the quality of food and drinking water, has been shown to be important to maintain battlefield readiness (Ishoy *et al.* 1999). In the Second World War, there were 235 cases of sand fly fever per 1000 personnel among troops based in the Persian Gulf (Hyams *et al.* 1995). In contrast, in the 1991 Gulf War, no cases of sand fly fever occurred in the US troops, partly because the troops were deployed in barren desert away from water, and the war occurred in the cooler months and partly because of improved vector control, including use of pesticides and insect repellent as a result of the application of exposure research findings from the Second World War experience (Hyams *et al.* 1995).

These examples of where exposure assessment has assisted in reducing disease rates during deployment relate to infectious diseases. For other types of environmental hazards, such as chemical, physical or radiological hazards, where the exposure pathways are less well defined, where there may be a longer latency period and the connection between the exposure and the disease is not well established, exposure assessment becomes much more challenging. This is particularly problematic where exposure may give rise to a health effect through an indirect pathway, such as a metabolite (Kipen & Fielder 2002).

3. METHODS USED FOR GULF WAR EXPOSURE DATA COLLECTION

Table 1 shows the major Gulf War exposures which have been investigated in relation to health effects in the Gulf War literature and references the main studies which have investigated each of these exposures. Self-report has been by far the most common exposure-assessment method used in these studies. This is not

surprising because gathering exposure data during battle has not usually been a major priority, as there are usually more urgent and immediate concerns.

Exposure was self-reported in 21 of the 29 studies of Gulf War veterans' health referenced in table 1 below. Sixteen of the 21 studies used a postal questionnaire, two of the others used telephone questionnaires and three of the studies gathered exposure data from face to face interviews. In most of these cases, veterans were asked to identify exposures from a list, usually as 'yes' or 'no'. In a few cases, a semi-quantitative estimation of level of exposure was sought, e.g. number of days exposed to the smoke and oil cloud (SMOIL).

Some of the studies in table 1 used more objective exposure data. In four of the studies (Fukuda *et al.* 1994; Poirier *et al.* 1998; Hooper *et al.* 1999; McDiarmid *et al.* 2004), exposure was estimated from personal exposure measurements including biological monitoring data, notably for DU (McDiarmid *et al.* 2004). Poirier *et al.* (1998) measured personal polycyclic aromatic hydrocarbons (PAH) exposure and DNA adducts and urinary 1-hydroxypyrene glucuronide in soldiers who had been in Germany and then went to Kuwait during the SMOIL episode.

Other studies used models to predict exposure to SMOIL (Lange *et al.* 2002; Smith *et al.* 2002a,b; Bullman *et al.* 2005) or to predict exposure to nerve gas from weapons destruction by the US troops at Khamisiyah (Smith *et al.* 2002b). Troop units were located using geographical information (GIS) systems and their positions compared to the exposure model. Accuracy in the use of modelled data depends on, however, the completeness and quality of troop deployment records, which can be difficult to verify *post hoc* for an individual.

4. HOW DOES QUESTIONNAIRE ADMINISTRATION AFFECT EXPOSURE ASSESSMENT?

There are no standardized, validated questionnaires used to assess veterans' chemical and environmental exposure in a war zone, such as the Gulf War. Such studies have usually developed their own exposure questionnaire(s), often drawing on those used in previous studies and modifying the questions for the particular circumstances (Unwin *et al.* 1999; Glass *et al.* in press). This is in contrast to the validated questionnaires such as the Short Form Health Survey (SF-36), Composite International Diagnostic Interview (CIDI), Posttraumatic Stress Disorder Checklist (PCL) and General Health Questionnaire (GHQ), which have been used to assess health outcomes.

There is evidence from the occupational literature that the interview type may affect the exposures that are reported. Face to face interviews have been shown to be more reliable than postal questionnaires (Blatter *et al.* 1997); and telephone interviews have been shown to give comparable results to self-administered postal questionnaires (van Ooijen *et al.* 1997).

As with health outcome questionnaires, exposure questionnaires must be piloted (Stewart *et al.* 2002) including the layout of the questionnaire and questions themselves. This is discussed in more detail elsewhere (Nieuwenhuijsen 2005). A pilot study has been

Table 1. Potential Gulf War exposures and the studies which have investigated them.

exposure	study reference
<i>war-related exposures</i>	
smoke and oil cloud (SMOIL)	Haley & Kurt (1997), Joseph (1997), The Iowa Persian Gulf Study Group (1997), Bell <i>et al.</i> (1998), Goss Gilroy Inc (1998), Kroenke <i>et al.</i> (1998), Poirier <i>et al.</i> (1998), Proctor <i>et al.</i> (1998), Ishoy <i>et al.</i> (1999), McCauley <i>et al.</i> (1999), Petruccielli <i>et al.</i> (1999), Unwin <i>et al.</i> (1999), Kang <i>et al.</i> (2000), Cherry <i>et al.</i> (2001), Lange <i>et al.</i> (2002), Wolfe <i>et al.</i> (2002), Smith <i>et al.</i> (2002a,b), Boyd <i>et al.</i> (2003), Wessely <i>et al.</i> (2003), Glass <i>et al.</i> (in press)
chemical warfare agents including nerve gas and mustard gas	Haley & Kurt (1997), The Iowa Persian Gulf Study Group (1997), Bell <i>et al.</i> (1998), Goss Gilroy Inc (1998), Kroenke <i>et al.</i> (1998), Proctor <i>et al.</i> (1998), Engel <i>et al.</i> (1999), Ishoy <i>et al.</i> (1999), McCauley <i>et al.</i> (1999), Unwin <i>et al.</i> (1999), Kang <i>et al.</i> (2000), McCauley <i>et al.</i> (2002), Smith <i>et al.</i> (2002b), Boyd <i>et al.</i> (2003), Stuart <i>et al.</i> (2003), Bullman <i>et al.</i> (2005), Glass <i>et al.</i> (in press)
wearing chemical protective clothing/respirators	Goss Gilroy Inc (1998), Unwin <i>et al.</i> (1999), Kang <i>et al.</i> (2000), Boyd <i>et al.</i> (2003), Glass <i>et al.</i> (in press)
depleted uranium including being inside destroyed Iraqi tanks	Haley & Kurt (1997), Goss Gilroy Inc (1998), Kroenke <i>et al.</i> (1998), Hooper <i>et al.</i> (1999), Ishoy <i>et al.</i> (1999), Kang <i>et al.</i> (2000), McDiarmid <i>et al.</i> (2004), Glass <i>et al.</i> (in press)
smoke from burned excrement/waste	Goss Gilroy Inc (1998), Proctor <i>et al.</i> (1998), Ishoy <i>et al.</i> (1999), Petruccielli <i>et al.</i> (1999), Unwin <i>et al.</i> (1999), Kang <i>et al.</i> (2000), Boyd <i>et al.</i> (2003)
exhaust fumes including use of tent heaters	Haley & Kurt (1997), Bell <i>et al.</i> (1998), Goss Gilroy Inc (1998), Kroenke <i>et al.</i> (1998), Proctor <i>et al.</i> (1998), Ishoy <i>et al.</i> (1999), Unwin <i>et al.</i> (1999), Wolfe <i>et al.</i> (2002), Boyd <i>et al.</i> (2003), Wessely <i>et al.</i> (2003), Glass <i>et al.</i> (in press)
<i>job-specific exposures</i>	
petroleum products including fuels, paints and solvents inhalation, skin and on ground	Haley & Kurt (1997), Joseph (1997), The Iowa Persian Gulf Study Group (1997), Bell <i>et al.</i> (1998), Goss Gilroy Inc (1998), Kroenke <i>et al.</i> (1998), Ishoy <i>et al.</i> (1999), McCauley <i>et al.</i> (1999), Petruccielli <i>et al.</i> (1999), Unwin <i>et al.</i> (1999), Kang <i>et al.</i> (2000), Cherry <i>et al.</i> (2001), Wolfe <i>et al.</i> (2002), Boyd <i>et al.</i> (2003), Wessely <i>et al.</i> (2003), Glass <i>et al.</i> (in press)
chemical agent resistant coating (CARC) paint (contains isocyanates)	Haley & Kurt (1997), Kroenke <i>et al.</i> (1998), Kang <i>et al.</i> (2000), Glass <i>et al.</i> (in press)
microwaves and radar	Kroenke <i>et al.</i> (1998), Ishoy <i>et al.</i> (1999), Kang <i>et al.</i> (2000), Boyd <i>et al.</i> (2003)
<i>preventive health measures</i>	
pesticide use (insecticides and rodenticide) including flea collars and use of pesticide treated clothing and bedding	Haley & Kurt (1997), The Iowa Persian Gulf Study Group (1997), Bell <i>et al.</i> (1998), Goss Gilroy Inc (1998), Kroenke <i>et al.</i> (1998), Proctor <i>et al.</i> (1998), Ishoy <i>et al.</i> (1999), McCauley <i>et al.</i> (1999), Unwin <i>et al.</i> (1999), Hotopf <i>et al.</i> (2000), Kang <i>et al.</i> (2000), Cherry <i>et al.</i> (2001), Wessely <i>et al.</i> (2003), Glass <i>et al.</i> (in press)
insect repellent particularly DEET-based repellents	Haley & Kurt (1997), Joseph (1997), Bell <i>et al.</i> (1998), Goss Gilroy Inc (1998), Kroenke <i>et al.</i> (1998), Proctor <i>et al.</i> (1998), McCauley <i>et al.</i> (1999), Ishoy <i>et al.</i> (1999), Unwin <i>et al.</i> (1999), Kang <i>et al.</i> (2000), Cherry <i>et al.</i> (2001), Glass <i>et al.</i> (in press)
<i>hazards from the environment</i>	
desert sand	Joseph (1997), Ishoy <i>et al.</i> (1999), McCauley <i>et al.</i> (1999), Petruccielli <i>et al.</i> (1999), Boyd <i>et al.</i> (2003), Glass <i>et al.</i> (in press)
infectious agents	Haley & Kurt (1997), Joseph (1997), The Iowa Persian Gulf Study Group (1997), Fukuda <i>et al.</i> (1998), Boyd <i>et al.</i> (2003)
local, contaminated or non-military issue foods	Goss Gilroy Inc (1998), Kroenke <i>et al.</i> (1998), Proctor <i>et al.</i> (1998), Ishoy <i>et al.</i> (1999), McCauley <i>et al.</i> (1999), Unwin <i>et al.</i> (1999), Kang <i>et al.</i> (2000), Boyd <i>et al.</i> (2003), Glass <i>et al.</i> (in press)
non-military water (bathed, tooth brushed or drank)	Goss Gilroy Inc (1998), Kroenke <i>et al.</i> (1998), Ishoy <i>et al.</i> (1999), McCauley <i>et al.</i> (1999), Petruccielli <i>et al.</i> (1999), Kang <i>et al.</i> (2000), Boyd <i>et al.</i> (2003), Glass <i>et al.</i> (in press)
mammal, reptile, scorpion or insect bites	Ishoy <i>et al.</i> (1999), McCauley <i>et al.</i> (1999), Petruccielli <i>et al.</i> (1999), Boyd <i>et al.</i> (2003), Glass <i>et al.</i> (in press)
extremes of heat and cold	Joseph (1997), Goss Gilroy Inc (1998), McCauley <i>et al.</i> (1999), Petruccielli <i>et al.</i> (1999), Boyd <i>et al.</i> (2003)

reported for most of the major Gulf War studies (The Iowa Persian Gulf Study Group 1997; Unwin *et al.* 1999; Cherry *et al.* 2001; Ikin *et al.* 2004). Piloting is important to ensure that instructions are clear and unambiguous. For example, if a person is asked to identify their tasks during a conflict, they may identify their personal activities or the unit's or ship's tasks depending on how the question is phrased. For example, workers on a supply ship may answer yes to the question 'Did you do refuelling?' because this was

done on the ship, even though they were not personally involved in this activity.

In most of the Gulf War veterans' studies referred to in table 1, exposures were presented as a checklist and this is in line with much of the occupational epidemiology literature. Recognition appears to be easier than recall for most work exposures so that accurate recall of exposure improves when prompted with specific names (Engel *et al.* 2001). Recall is better for brand names or nicknames than for chemical names

(Teschke *et al.* 1994; Stewart *et al.* 2002). In open-ended interviews or questionnaires, recall has high specificity, (few false positives or incorrect recognition of a substance) but low or variable sensitivity (more false negatives or failure to identify an exposure) (Bond *et al.* 1988; Joffe 1992; Fritschi *et al.* 1996). Subjects may fail to recall exposures for many reasons, e.g. they feel threatened by the exposure or may focus on an example rather than understand that it was merely an illustration (Stewart *et al.* 2002). However, workers are clearly capable of a qualitative ranking of exposure to some materials, which compares well with an external standard (doPico 1982; Teschke *et al.* 1989).

Questions that are impossible or difficult to answer should be screened out, e.g. asking subjects to average an exposure for a variable task, e.g. how many hours per day they were exposed to exhaust fumes. Questions asking for subjective evaluation are also undesirable e.g. whether there was a strong smell, as are questions that try to estimate the extent of exposure. Such questions are often too complex, involving estimation of both the frequency and length of repeated exposure e.g. SMOIL exposure (Stewart *et al.* 2002). There is a body of literature from anthropology and psychology that deals with the way that questions are perceived and answered (Kahneman *et al.* 1982). The following are important considerations:

- (i) individuals tend to over simplify situations when assessing them, so that they may report exposure to SMOIL, since the SMOIL cloud blocked out the sun when in fact it was not at ground level and would not have been inhaled.
- (ii) information that is easily recalled is assumed to be more significant rather than just more accessible, e.g. experiencing chemical alarms is easily recalled where the use of pesticide treated uniforms would be less likely to be remembered.
- (iii) individuals are inevitably selective about the information that they use to make judgements, and tend to use that which chimes most strongly with their beliefs. This includes the preference for health effects from the Gulf War experience to be attributed to exposure to chemical or physical agents rather than to psychological stressors.

5. IS BELIEF IN EXPOSURE AN IMPORTANT FACTOR?

One difficulty with self report is that it does not allow us to distinguish between actual remembered experience and belief in the exposure (Boyd *et al.* 2003). Belief in past exposure to chemical warfare agents has been shown to correlate with current ill health (Unwin *et al.* 1999; Stuart *et al.* 2003). Boyd *et al.* (2003) point out that the number of days using a gas mask for 1–4 h, being wounded and using unsafe equipment correlates with stressful conditions and also with high numbers of symptoms. However, it is not clear whether the individual exposure(s), the stressful experience as a whole, or memory of the events is the important factor.

6. IS THERE EXPOSURE RECALL BIAS?

Recall bias or differential recall can be problematic in self-reported exposure assessment. This has been pointed out by several Gulf War investigators (Bell *et al.* 1998; Ishoy *et al.* 1999; McCauley *et al.* 1999; Cherry *et al.* 2001; Wessely *et al.* 2003; Glass *et al.* in press). Recall bias occurs where there is *post hoc* attribution of exposure more frequently by those who are sick than by those who are well (Boyd *et al.* 2003). This may be a result of personality differences, e.g. individuals with high negative affectivity are more likely to be hyper-vigilant in scanning the environment, particularly in ambiguous environments, and to report more subjective health effects (Dalton & Hummel 2000). As Cherry *et al.* (2001) pointed out, the bias can be in perception, recall or reporting, and generally speaking we cannot identify which bias is operating. It may not be possible *post hoc* to identify whether those who are symptomatic recall more exposures or really were more exposed, if we rely solely on self-report of exposure. Recall bias has been identified as occurring in the Gulf War veterans' health studies (McCauley *et al.* 1999; Wessely *et al.* 2003). Some studies have suggested that recall bias was not widespread (Glass *et al.* in press) or is unlikely for specific remembered exposures, e.g. manure and cockroaches (Ishoy *et al.* 1999), or immunizations (Cherry *et al.* 2001).

Exposure might be expected to be uniform within a unit or ship. If there are within-unit or within-ship differences in exposure reporting and these correlate with caseness, this may be evidence of recall bias. However, this approach should be used with caution. The evidence from occupational studies is that between any two workers with the same job title, the actual mix of tasks and the time spent on each may vary. For a single worker, there will be variations in the mix of tasks and the time spent on each during the relevant time period. Such between-worker and within-worker differences can lead to considerable differences in exposure even for workers who had the same job title. This is particularly true in a war environment where troops may move between units and into several different environments over a short period of time.

Knowledge of the tasks performed may be more important than the job title (Lemasters *et al.* 1985). For example, exposures may vary within an apparently uniform work group as a result of factors such as differing seniority (Gomez 1996). Our data showed that the experienced Australian Gulf War veterans (who had been on a previous deployment) reported more exposures than those for whom the Gulf War was their only deployment (Glass *et al.* in press). This may be true differential recall as more experienced subjects may notice or remember more deployment exposures than first-timers, or it may result from more experienced veterans genuinely being more likely to be exposed to more environmental insults due to their previous experience in such situations.

Registry studies may be particularly prone to this form of bias, as veterans who experienced SMOIL or intense combat or were close to Khamisiyah when it was demolished have been shown to be more likely to join a Veterans' Register. Therefore, exposure (or higher recall of exposure) can predict entry to such

studies. This has also been characterized as health care-seeking behaviour (Smith *et al.* 2002b).

Recall bias may not be a result of over-reporting by those who were symptomatic. In case-control studies in the workplace, exposure reporting may be more accurate by cases than by controls, as a result of under-reporting by controls (Ahlborg 1990). In other studies, cases may appear to over-report since infrequent or low exposures were not reported by controls but were included by cases (Blatter *et al.* 1997). In support of this contention, there is evidence of under-reporting of low-level/short-term exposures by workers when compared to expert assessment (Teschke *et al.* 1994). False positives (recall of an area of work not recorded by management) were rare (Bond *et al.* 1988). In the Gulf War, those who were symptomatic may report exposure to petroleum products which those who were non-symptomatic discounted as a normal part of life and may be less likely to report later.

7. HOW STABLE IS RECALL OVER TIME?

Most of the Gulf War veterans' studies started some years after the conflict e.g. the UK studies started in 1996 (Hotopf & Wessely 2005) and in Australia in 2000 (Ikin *et al.* 2004). In these studies, veterans were asked to recall exposures remote in time, up to a decade previously. Several occupational epidemiology studies have examined the ability of subjects to recall the details of exposure over time. Evidence from the literature suggests that subjects can recall their job histories and duties accurately over 10–15 years, compared to objective records, but that accuracy declines with increasing numbers of jobs, with increasing years since the job was held, with short-duration jobs and with lower levels of education (Keating *et al.* 1950; Baumgarten *et al.* 1983; Rosenberg *et al.* 1987; Bond *et al.* 1988; Bourbonnais *et al.* 1988). Thus, we might expect the Gulf War veterans to under-report short-term exposures which took place several years ago.

In the context of the Gulf War, test-retest on a subset of veterans found moderate agreement for several exposures and this finding did not depend on caseness (McCauley *et al.* 1999; Wolfe *et al.* 2002). There was a similar variability in test-retest kappa statistics, when repeating the same questionnaire 2–4 years apart (Wessely *et al.* 2003). So, this suggests that exposure recall for only a few years into the past, especially in the earlier Gulf War studies, may not have been a major problem, but may become more so in future studies, now that 15 years have elapsed since the Gulf War.

8. DO MEDIA REPORTS INFLUENCE EXPOSURE REPORTING?

Peaks of self-referrals by Gulf War veterans to the US Department of Veterans' Affairs clinical registries for assessment of health problems have been found to correlate with Gulf War media stories and US Department of Defense reports (Smith *et al.* 2002b). Therefore, this raises the question of whether exposure reporting may also be influenced by such reports. However, no observed correlations between

self-reported exposures and media interest have been identified in another study (McCauley *et al.* 1999). Perhaps trivial exposures are recalled during periods of media interest, but not at other times, especially when these exposures are presented with several other exposures.

9. HOW CAN ACCURACY OF RECALL BE VERIFIED?

Self-reported exposures are difficult to verify, but some of the Gulf War studies have tried to do this by comparing self reports with modelled exposure, based on actual measurements. A modest correlation between self-reported exposure and modelled SMOIL exposure has been demonstrated (Lange *et al.* 2002). In another study, the correlation between self-reported exposure and modelled SMOIL improved if frequency, intensity and duration were taken into account (Wolfe *et al.* 2002). Use of the refined plume model in 2000 increased the precision of the model's application to (smaller) company-based rather than (larger) battalion-based assessment (Bullman *et al.* 2005). Some studies compared the recall of immunizations for those with and without records and showed that they were broadly similar (Cherry *et al.* 2001; Kelsall *et al.* 2004b; Hotopf & Wessely 2005).

Significant over-reporting of exposure has been identified by comparing self reports with location (The Iowa Persian Gulf Study Group 1997; Glass *et al.* in press) or on period served in the Gulf, e.g. veterans not deployed during the actual combat period reported exposure to anti-biological warfare vaccines, PB and chemical warfare agents which were improbable exposures (The Iowa Persian Gulf Study Group 1997; McCauley *et al.* 1999). This may be more of a problem with more highly publicized exposures.

Replication of some part of the data collection and the use of fictitious exposure choices to check reliability is recommended to investigate this problem (Armstrong *et al.* 1992). In the Gulf War context, the inclusion of unlikely vaccinations such as smallpox in a list could be used. Comparison of self-reported SMOIL exposure for veterans reporting respiratory health effects and health effects with little biological plausibility for association with SMOIL have also been used to check accuracy of recall (Lange *et al.* 2002). Chemical agent resistant coating (CARC) paint was only used by one unit of the US soldiers (and some civilians from the USA), and indeed only 1.3% of Australian veterans reported such contact suggesting that over-reporting was not widespread (Glass *et al.* in press).

Alternatively, test and retest procedures can be used to check reliability. In one study, exposure recall was measured and retested a few weeks later. Only exposure to PB was highly reliable, while there was moderate reliability for insect repellents, pesticide use and belief in exposure to chemical warfare agents (McCauley *et al.* 1999). In a longitudinal study, those Gulf War veterans who were sick tended to increase the number of exposures they reported over time (Wessely *et al.* 2003). This again demonstrates the need to document exposures early.

Other sources of data that could be used for exposure verification are the ships' logs (Glass *et al.* in press) or the UK army commanders' diaries (Capleton *et al.* 2001). Such sources contemporaneously document major events at unit or ship level. However, the data are patchy and are usually not recorded in a systematic way for research purposes and considerable manual effort is needed to collate them and to relate the data to individual service personnel. A review of available exposure data in military records in the UK found that linkage systems for exposure data are also usually poor, so these would need to be improved to be useful in health studies (Capleton *et al.* 2001). In addition, individuals do unauthorized things which may not be recorded, but nevertheless would be self-reported, e.g. use of flea collars (Haley & Kurt 1997) or use of locally obtained pesticides (Presidential Advisory Committee on Gulf War Veterans' Illnesses 1996), so it might be difficult to decide which source of data most closely reflects the true exposure.

10. IS GULF WAR ILLNESS ACCOUNTED FOR BY GULF WAR SPECIFIC EXPOSURES?

It has been pointed out that veterans have reported increased symptoms after most modern wars (Hyams 1999). It is possible that there is a common aetiology for these increased symptoms across different deployments, such as battlefield stress. A UK study found that active combat troops were not specially at risk of ill health compared to combat support troops, despite more exposure to chemical and physical agents, suggesting that battlefield stressors are more likely to be the causative agent (Ismail *et al.* 2000).

If, however, there are exposures that result in symptoms specific to a conflict then the exposure(s) may also be specific. In the Australian Gulf War study six exposures were reported significantly more frequently by veterans of the Gulf War than by the Australian veterans of other active deployments. These were exposure to dust or SMOIL or chemical warfare agents, the use of chemical protective clothing or respiratory protective equipment, and entering or inspecting enemy equipment (Glass *et al.* in press). UK Gulf War veterans were also more likely than a Bosnian War veterans' comparison group to report having heard chemical alarms and to believe that they had been exposed to chemical warfare agents (Unwin *et al.* 1999). Thus, there are several exposures that were specific or much more common to the Gulf War but these have not been isolated in several Gulf War veterans' studies.

11. WHAT PROBLEMS DO MULTIPLE EXPOSURES BRING?

As we have seen, many exposures have been investigated in the Gulf War veterans' studies. The relatively high number of exposures investigated results in multiple comparisons of exposure-risk relationships, hence there is an increased probability of a Type 1 error (Kroenke *et al.* 1998; Ishoy *et al.* 1999). Most studies have, however, been unable to identify a single exposure as the most important causative factor for the observed ill health (Kroenke *et al.* 1998). One study

group has identified a group of exposures which may act in concert (Haley & Kurt 1997), but this finding has not been replicated by other studies.

In many industrial situation workers are exposed to more than one hazard, e.g. benzene and other hydrocarbons in the petroleum industry or solvents and manual handling in dry cleaning (Ahlborg 1990). In these circumstances, the attribution of risk to one or other exposure is problematic. Such co-exposures were common in the Gulf War, where one exposure may merely be a marker for another perhaps causal exposure, e.g. those in the thick of the battle will be more likely to have experienced SMOIL, possible DU exposure, tent heater exhaust, and stressors such as seeing comrades killed. There is probably multi-co-linearity for a unit's physical exposures because of common time and place but there is also likely to be co-linearity with psychosocial variables such as morale (Hotopf & Wessely 2005).

Examples from the Gulf War literature include the number of days with a gas mask on for 1–4 h, correlating with stressful conditions, PB and immunizations (Boyd *et al.* 2003). Cherry *et al.* (2001) calculated correlation coefficients and showed that several of 14 exposures correlate strongly. Similar correlations were found in other studies (Unwin *et al.* 1999; Kelsall *et al.* 2004b, 2005). Therefore, this may mean that it will not be possible to tease out which specific exposure may be the main agent in bringing about later disease, apart from considerations of biological plausibility.

12. IS THERE EXPOSURE MISCLASSIFICATION?

The lack of identification of a single exposure factor may reflect a genuine lack of any association or inadequate tools to measure exposure. Non-differential misclassification between study groups, i.e. misclassification not associated with the health outcome of interest, tends to bias results towards the null value or reduce the effect size (Copeland *et al.* 1977). This will occur when individuals who were not deployed were included with the Gulf War veterans. Non-differential misclassification is particularly important where exposure prevalence is low (Benke *et al.* 1997). Careful exposure assessment is needed to ensure that we do not miss true exposure–outcome associations (Type 2 error). Bullman *et al.* (2005) pointed out that in their study, reclassification of only three brain cancer cases to the unexposed group would have resulted in the observed risk becoming statistically non-significant. In a study of hospitalizations among troops in the vicinity of Khamisiyah, an early model identified 20 000 troops within 50 km of Khamisiyah. A later model of exposure removed half of these, i.e. many of the troops who had been classified as exposed were reclassified as not exposed. In addition, identification of plume direction suggested that some of those originally classified as not exposed could, in fact, have been exposed (McCauley *et al.* 2002), suggesting a large potential for exposure misclassification in such studies.

Further, if only those workers who are highly exposed are at risk of ill health, grouping them with others exposed infrequently to only low levels will result

in non-differential exposure misclassification and a consequent reduction in observed risk estimates (Copeland *et al.* 1977).

Differential misclassification, i.e. misclassification that is associated with the ill health under investigation, arises from a biased estimate of exposure, and can result in an increase or decrease in the observed risk estimate. Recall bias causes differential misclassification, i.e. those veterans who are symptomatic may recall more or different exposures than those who are unaffected. Alternatively, those who are unaffected may under-report exposures. In this case, the misclassification results in an increased odds ratio for the exposure in question.

13. WHY MIGHT EXPOSURE AFFECT INDIVIDUAL VETERANS DIFFERENTLY?

Rothman & Greenland (2005) distinguish between a 'cause' and a 'sufficient cause'. In other words, there may be a need for several factors acting before a disease develops in an individual and these may include genetic factors as well as exposures. Not all smokers develop lung cancer, not all Gulf War veterans have increased symptoms.

The same exposure may have more or less severe effects on different people as a result of their genetic make up (Smith & Ebrahim 2003). In studies of sheep dipper, increased symptoms were found in those who had a genetic variant of paraoxonase, so that organophosphates (OP) were hydrolysed more slowly (Mackness *et al.* 2003). Thus, it may be important to identify a subset of a population for whom an exposure may have significant health effects because of genetic susceptibility, but the majority of those exposed may not be affected or may be less severely affected. Differences in the proportion of alleles in the Gulf War veterans and a comparison population have been found, although there was no difference in the proportion between symptomatic and asymptomatic groups (Hotopf *et al.* 2003). Another investigator found differences in the frequency of different paraoxonase alleles between the symptomatic and asymptomatic veterans (Haley *et al.* 1999).

Exposure to one substance may amplify, exacerbate or make manifest the effects of a concurrent exposure, e.g. the neurological damage caused by exposure to *n*-hexane is amplified with simultaneous exposure to other substances such as methyl ethyl ketone (Anonymous 2001). Haley & Kurt (1997) pointed out that several Gulf War exposures, PB, OP pesticides and DEET target the neurotransmission system, specifically cholinesterase. Thus, the experience of the combination of exposures might be more significant than a single exposure alone.

14. HOW DO WE CHOOSE A RELEVANT EXPOSURE METRIC?

In recent years, there has been an emphasis on carrying out quantitative exposure assessments partly because evidence of an exposure-response strengthens the case for a causal relationship between the exposure and the risk. However, the relevant exposure metric (the way we define the characteristics of the exposure) may not be obvious. The correct metric for a particular

substance may include concentration, duration and frequency dimensions, but for most exposures, even those which have been thoroughly investigated such as benzene, the interactions of these different dimensions is not fully understood, so the definitive exposure metric may not be identified for most exposures. In the case of benzene, despite considerable research findings showing it as a cause of leukaemia, it is not yet known whether duration of exposure in years, intensity of exposure (average daily parts per million) or cumulative exposure, intensity multiplied by duration (parts per million-years), is the more appropriate metric (Glass *et al.* 2003).

In the Gulf War studies, it is difficult to determine the important exposures and the most appropriate exposure metrics. For exposure to SMOIL several metrics have been used. Simple metrics based on recall include exposed yes/no (Kelsall *et al.* 2004a) or low, medium or high exposure based on an algorithm of number of days and hours per day (Kelsall *et al.* 2004a). More complicated metrics using modelled data include: number of days exposed over a threshold (Lange *et al.* 2002); number of days exposed multiplied by modelled average total suspended particulate (TSP), number of days at TSP 0.26 mg m^{-3} or more times the average TSP for those days' exposure; presence or absence of TSP 0.26 mg m^{-3} or greater (Bullman *et al.* 2005). More research is needed to identify which of these (or others as yet not thought of) are the most appropriate exposure metric.

15. POSSIBLE FUTURE EXPOSURE-ASSESSMENT METHODS

In view of these problems; a more objective alternative to self-reported exposures in Gulf War studies is desirable. What can be learnt from the occupational epidemiological literature? From an exposure-assessment point of view, occupational epidemiological studies usually fall into two groups, those in the general population, usually case-control studies, which are not really relevant here, and those in a particular industry, usually cohort studies.

Exposure can be deduced from job histories using pre-prepared job exposure matrices (JEMs) which can be specific to an industry (Kauppinen & Partanen 1988; London & Myres 1998). In JEMs, the cell contents may be in the form of a probability of exposure (low, medium, high) or extent of exposure (exposed/not exposed, ever/never, low/medium/high). The use of such matrices has been shown to be an unbiased, quick and relatively cheap way of assessing the exposure of large groups of subjects (Ahrens *et al.* 1993). In most cases, if a JEM is sensitive (low false negatives) it will have low specificity (high false positives) and *vice versa* (Plato & Steineck 1993).

An alternative method of exposure assessment is to use experts singly or in panels, to evaluate likely exposures from interviews/questionnaires. Experts examine the occupational histories of cases and controls and recommend one or more job-specific modules (JSMs), which are used in extended interviews. The answers are used to assess exposure on an ever/never basis or as a probability with or without

semi-quantitative weightings (Siemiatycki *et al.* 1981; Gerin *et al.* 1985; Gomez *et al.* 1994; Stewart *et al.* 1998). Expert evaluations of interviews compare well with measured exposure data, depending on the expertise of the experts (Clavel *et al.* 1993; Stewart & Stewart 1994; Benke *et al.* 1997). Expert evaluations have been found to be more sensitive and specific than the application of an *a priori* JEM (Siemiatycki *et al.* 1989; Rybicki *et al.* 1997; Tielemans *et al.* 1999).

It would be possible to construct a JEM or to prepare military JSMs probing for specific exposures of interest. Military experts would be needed to identify exposures and attribute them to specific groups of personnel. Several of the exposures listed in Gulf War questionnaires are commonly encountered during periods of training, during military exercises, during peacemaking and peacekeeping, as well as during active deployments to war zones. These include engine exhaust, petroleum products and pesticides (Glass *et al.* *in press*). Of course, exposure may be higher or more frequent during the heat of battle when normal health and safety precautions may assume a secondary role to other considerations. Guidelines have been developed for military personnel to estimate exposure to chemical hazards for deployed personnel; however, record keeping during conflict will probably continue to be a low priority (Hauschild & Lee 2004).

Occupational exposure can often be more precisely characterized in studies undertaken at one site or within one industry group. In these cases, there have been a variety of exposure classification schemes depending on the amount of information available:

- (i) a qualitative exposure assessment, yes/no, e.g. based on classification by management (Coggon *et al.* 1989);
- (ii) a probability estimate predicting the likelihood of a job group having exposure to a particular substance and the likelihood of exposure for any particular holder of that job title (Stewart & Stewart 1994);
- (iii) a semi-quantitative assessment, from questionnaires or from knowledgeable workers in the area (Greenberg & Tamburro 1981); or
- (iv) quantitative exposure assessment where individuals are assigned to homogenous exposure groups or exposure zones on the basis of expert judgement (Corn & Esmen 1979). The exposure groupings can be modified on the basis of exposure monitoring results, thus giving a more defensible division between subjects (Kromhout *et al.* 1987). These kinds of data have seldom been available in the Gulf War veterans' studies except as modelled data.

There is variation in exposure as a result of between-worker variability and within-worker variability. Although occupational exposure data has shown that day-to-day variability is generally greater than between-worker variability (Kromhout *et al.* 1993), the typical lognormal distribution of exposure may include one or more workers who were normally more highly exposed than the remainder of the group, perhaps because of the way that the individual did the job or their personal

characteristics, e.g. height. The group average exposure would not, under these circumstances, be a true representation of the individual's exposure and it may be precisely these workers who become symptomatic. Between-worker variability, i.e. the within group distribution of exposure, can be due to plant, occupation, day-to-day variation, seasonal variation or individual work practices (Heederik & Hurley 1994).

Regression analysis has shown that environment (indoor versus outdoor) and process (continuous versus intermittent) usually accounts for much of the within-worker variance (Kromhout *et al.* 1993). In general, exposure during deployments, such as the Gulf War, is usually in the open air and may well be intermittent. Quantitative exposure modelling such as that carried out for chemical weapons fallout or SMOIL exposure cannot take into account these between veteran differences in exposure, and in addition will only be as good as the record keeping at the time that identifies where a particular individual was located.

The last possibility for objective exposure assessment would be a *post hoc* biological measurement such as salivary cotinine for nicotine intake or uranium in urine measurements for veterans with DU exposure, such as from shrapnel (McDiarmid *et al.* 2004). Biological monitoring for most Gulf War exposures has not been developed and is not relevant to most of the exposures of interest. Pre- and post-war measurements would be needed for exposures also encountered outside the war zone, and only those exposures with half-lives longer than the war period would be suitable.

16. CONCLUSIONS

Given the vagaries of the battlefield during the Gulf War and other war deployments, pre-prepared JEMs are unlikely to be sensitive to individual variations in exposure. In addition, there will be exposures such as to SMOIL that could not have been foreseen prior to the war. JSMs are impractical as instruments to screen large numbers of veterans for several different exposures. They may be useful for selected exposures, for small numbers of individuals, as is bio-monitoring.

The most likely practical choice for exposure assessment in veterans' health studies is to continue to use piloted and validated questionnaires to record self-assessed exposure during deployments, either during or fairly soon after exposure. There is some evidence that interview administered questionnaires are preferable, but this is expensive compared to postal questionnaires and the evidence is not strong. There is good evidence to suggest that we should build in checks of reliability which might include building in dummy or unlikely exposure variables; retesting after a period of time for repeatability; examining how reported exposures compare with any records that do exist, such as modelled exposure data, to known timeframes or geographic variations, or comparing reporting consistency for individuals who deployed together, e.g. on one ship or as predicted from GIS data. This is, in essence what has been happening in the Gulf War literature, where studies coming later in time are

building upon the accumulated experience of previous researchers and improving the process of exposure assessment. There is however, we believe, scope for sharing of exposure questionnaire layout and question wording designed to derive an optimum and consistent format.

The application of any of these exposure methods will be most effective if planned before deployment and the investigations take place during the deployment or soon after veterans return from theatre.

Despite the numerous studies that have examined the relationship between the various Gulf War exposures and health outcomes, there is little consensus on which, if any, of the many exposures experienced in the Gulf War have been responsible for the excess symptomatology found in Gulf War veterans from many different countries. While some associations have been found in some studies, many have not been replicated in other studies, and differences in exposure assessment and resultant exposure misclassification may explain at least part of this lack of consistency.

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