Toxicological assessments of Gulf War veterans

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Concerns about unexplained illnesses among veterans of the 1991 Gulf War appeared soon after that conflict ended. Many environmental causes have been suggested, including possible exposure to depleted uranium munitions, vaccines and other drugs used to protect troops, deliberate or accidental exposure to chemical warfare agents and pesticides and smoke from oil-well fires. To help resolve these issues, US and UK governments have sought independent expert scientific advice from prestigious, independent scientific and public health experts, including the US National Academies of Science and the UK Royal Society and Medical Research Council. Their authoritative and independent scientific and medical reviews shed light on a wide range of Gulf War environmental hazards. However, they have added little to our understanding of Gulf War veterans' illnesses, because identified health effects have been previously well characterized, primarily in the occupational health literature. This effort has not identified any new health effects or unique syndromes associated with the evaluated environmental hazards. Nor do their findings provide an explanation for significant amounts of illnesses among veterans of the 1991 Gulf War. Nevertheless, these independent and highly credible scientific reviews have proven to be an effective means for evaluating potential health effects from deployment-related environmental hazards.

Keywords: veterans; pesticides; uranium; pyridostigmine bromide; sarin

1. INTRODUCTION

Initial jubilation among Coalition partners over the decisive nature of the 1991 Gulf War with remarkably few casualties gave way in the following years to concerns that veterans of that conflict were suffering from new or unexplainable illnesses. Both US and UK governments responded in part by seeking expert scientific advice from prestigious, independent scientific and public health experts, including the National Academies of Science (NAS) in the US and the Royal Society and Medical Research Council (MRC) in the UK. Taken as a whole, this scientific and medical review and advice has shed light on a wide range of environmental risk factors associated with that deployment.

The US Department of Veterans Affairs (VA) is uniquely responsible for providing a wide range of benefits to nearly 26 million US veterans and their families. This includes the approximately 697 000 US men and women service members who served in the Gulf War build-up and combat from August 1990 to June 1991. Major VA benefits include healthcare and disability compensation for illnesses and injuries related to military service. Disability compensation provides monthly monetary benefits, in amounts established by Congress and based upon the degree of disability, to veterans disabled by service-connected injuries or diseases, that is, for illnesses or injuries shown to have been incurred or aggravated through military service. The delivery of effective healthcare and the provision of benefits by VA are both dependent on the identification

of health risks during military service. The demonstration of military health risks is often a contentious process, both scientifically and politically, as has been amply demonstrated by the Gulf War health debate.

To identify environmental and occupational health risks relative to veterans of the 1991 Gulf War, the United States VA has relied upon formal evaluations of peer-reviewed scientific literature by the independent and prestigious National Academy of Sciences Institute of Medicine (IOM). Under a US congressionally mandated process that began in 1998, the IOM has produced a series of rigorous and comprehensive scientific literature reviews for the majority of recognized Gulf War risk factors. Their occupational and environmental health findings remain authoritative, but they have added little to our understanding of Gulf War environmental hazards. This is because all the health effects they identified have been previously well characterized, primarily in the occupational health literature. Consistent with similar reviews from other countries including the UK, the exhaustive investigations by the IOM have not identified any new health effects or unique syndromes associated with postulated risk factors evaluated.

In this contribution I will review the results of this process, with particular focus on health issues related to putative environmental hazards encountered during the 1991 Gulf War. More detailed account of particular topic areas follow as separate contributions; this chapter is intended as an overview and summary.

(a) *Early environmental health concerns*

The relatively short 1991 Gulf War was seen as highly successful. Iraqi forces were quickly routed from

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One contribution of 17 to a Theme Issue 'The health of Gulf War veterans'.

Kuwait during a 4-day ground war with low casualties among Coalition troops. However, as reports emerged in 1992 and 1993 of increasing health problems, many Gulf War veterans and their supporters expressed concerns that their illnesses were the result of exposure to one or more hazardous agents during that conflict. Specific concerns included the first war-time use of special depleted uranium (DU) armour-piercing munitions, vaccines and other drugs used to protect troops, deliberate or accidental exposure to chemical warfare agents and smoke from oil-well fires ignited by retreating Iraqi troops.

In 1993, VA created a special voluntary Gulf War clinical registry, which by July 2005 had evaluated about 96 000 (about 14%) Gulf War veterans in this clinical surveillance programme. Principal findings were that these veterans are suffering from a wide variety of recognized illnesses, but no new or unique syndrome was identified (*Combined Analysis of the VA and DoD Gulf War Clinical Evaluation Programs 2002*). As the lead federal agency on Gulf War-related research, VA was responsible also for coordinating federally sponsored epidemiological and other relevant scientific studies in the USA. As of today, this coordinated approach has spent more than \$250 million for more than 200 Gulf War health-related research projects. However, as noted in the 2003 MRC report, '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.'

Because most VA benefits depend in part upon establishing a connection to military service, growing environmental health concerns put pressure on VA to determine which Gulf War hazards had caused specific illness and disease among these new veterans. Establishing service connection usually requires a simple medical review in the case of a veteran with an injury clearly related to military service, e.g. from a bullet or shrapnel wound. Establishing service connection can be much more contentious when the illness or injury involves a chronic disease possibly caused by environmental or occupational exposure that may have occurred years or decades in the past. For example, it can be difficult for a veteran to provide evidence that their leukaemia was specifically caused by exposure to benzene during their military service, in comparison to all other possible causes that they may have been exposed to over their lifetimes.

2. ROLE OF THE NATIONAL ACADEMY OF SCIENCES INSTITUTE OF MEDICINE

VA has long relied upon the independent scientific advice of the National Academy of Sciences Institute of Medicine (IOM) to help evaluate potential associations between specific health effects and environmental hazards encountered during various military deployments. An example of this advice are about a dozen diseases that VA has determined, based upon IOM's periodic literature reviews, to be automatically presumed as connected to exposure to Agent Orange and

other herbicides during the Vietnam War, and to the dioxin impurity some contained.

(a) *Formal veteran's health advisory role*

The NAS was established in 1863 with the signature of President Abraham Lincoln, to 'investigate, examine, experiment and report upon any subject of science or art' for agencies in the federal government. In 1970, the NAS created the IOM to provide independent, objective, authoritative, credible and timely scientific analyses on medical and health issues. The US Congress through US government agencies regularly seeks the IOM's unique scientific advice on a broad range of health-policy issues. The IOM does not compete for funding in response to federal requests for proposals.

The IOM has developed a highly formalized process designed to provide authoritative, objective and scientifically balanced answers to difficult public health questions of national importance. Their studies are conducted by independent committees of volunteer scientists composed of leading nationally and internationally recognized experts, selected by the IOM based on their expertise, good judgment and freedom from conflict of interests. Committee members serve as individuals, not as representatives of organizations or interest groups. Although some committee meetings may be opened to the public, committee findings and conclusions are based upon their review of the relevant scientific and medical literature, with a primarily focus on peer-reviewed materials. The IOM acknowledges that although peer review ensures high standards of quality, it does not guarantee the validity of a study or the ability to generalize its results. Therefore, committee members are expected to critically read each publication for relevance and quality before reaching conclusions.

Recognizing that even scientific subject matter experts inevitably bring their own biases and experiences, the IOM has specific procedures to ensure appropriate committee membership balance and to avoid real or perceived conflicts of interest. For example, a committee member would virtually never be put in the position of reviewing his or her own research—a safeguard that has been absent from the work of other 'expert' committees. Committee members are required to itemize in writing all professional, consulting and financial connections, as well as pertinent intellectual positions and any relevant public statements. Because potential committee members with professed bias, prejudice or significant preconceptions on the subject at hand are carefully excluded, IOM committee findings are usually considered to be independent and highly credible.

The IOM requires that a committee's formal findings and recommendations are evidence-based whenever possible and noted as only expert opinion when that is not possible, making them similar to 'Cochrane Reviews' in depending on a predetermined methodology and standards of evidence, albeit with a special focus on military and veteran health issues. Each IOM report undergoes extensive formal internal and peer review by a group of external experts who are anonymous to the committee, and whose names are revealed only once the study is published.

Table 1. Studies on Gulf War veterans' health issues by the National Academy of Sciences Institute of Medicine (IOM) (available online at www.nap.edu).

<i>'Gulf War & Health': congressionally mandated studies on Gulf War environmental risk factors</i>
'Gulf War and health: volume 1. Depleted uranium, pyridostigmine bromide, sarin, and vaccines.' 2000
'Gulf War and health: volume 2. Insecticides and solvents.' 2003
'Gulf War and health: updated literature review of sarin.' 2004
'Gulf War and health: volume 3. Fuels, combustion products, and propellants.' 2005
<i>Gulf War veteran's health: clinical and policy evaluations</i>
'Gulf War veterans: treating symptoms and syndromes.' 2001
'An assessment of the safety of the anthrax vaccine: a letter report.' 2000
'Protecting those who serve: strategies to protect the health of deployed US forces.' 2000
'Strategies to protect the health of deployed US forces: detecting, characterizing, and documenting exposures.' 2000
'Measuring the health of Persian Gulf veterans: workshop summary.' 1998
'Gulf War veterans: measuring health.' 1999
'Strategies to protect the health of deployed US forces: medical surveillance, record keeping, and risk reduction.' 1999
'National Center for Military Deployment Health Research.' 1999
'Adequacy of the VA Persian Gulf registry and uniform case assessment protocol.' 1998
'Adequacy of the comprehensive clinical evaluation programme: a focused assessment.' 1997
'Adequacy of the comprehensive clinical evaluation programme: nerve agents.' 1997
'Health consequences of service during the Persian Gulf War: recommendations for research and information systems.' 1996
'Health consequences of service during the Persian Gulf War: initial findings and recommendations for immediate action.' 1995

(b) IOM veterans' health reviews

The IOM's highly developed formal review process has proven invaluable to VA for establishing fair, scientifically based disability policies for veterans. Their unsurpassed reputation for objectivity, scientific integrity and independence means that their reports stand as authoritative even when their findings fail to please all stakeholders. By law and historical precedent, VA depends upon formal IOM reviews to help establish compensation policies for veterans exposed to Agent Orange, other herbicides and dioxin used in the Vietnam War, for veterans experimentally exposed to chemical warfare agents prior to 1975, and for veterans exposed to a wide variety of environmental hazards during the 1991 Gulf War. The IOM is also often requested to examine a wide range of general clinical issues, and since 1991, IOM has completed 17 independent reviews of Gulf War health issues (table 1).

Since IOM's Gulf War environmental health studies are designed to inform veteran disability compensation policies and to identify specific human diseases that may be associated with military environmental hazards, they primarily focus upon human studies,

supplemented by a thorough review of all relevant animal studies. They concentrate on scientific literature documenting long-term chronic and delayed health effects that are most relevant to potential disabilities. Their conclusions are applicable to specific exposures and diseases that may occur among military veterans. For example, the IOM's finding that dioxin exposure is not only a carcinogen, but is specifically associated with Hodgkin's disease led VA to establish a compensation policy specifically for veterans exposed to dioxin and who develop Hodgkin's disease.

Since the end of the 1991 Gulf War, at least 14 different committees have been established, both in the United States and the United Kingdom, to help evaluate Gulf War veteran health issues. However, the IOM's reputation for scientific rigour, independence from the political process, and freedom from bias has made it one of the most influential sources.

The UK MRC and Royal Society also achieve such an international stature and credibility, and together these sources have almost certainly had the greatest impact on our understanding of health issues among veterans of the 1991 Gulf War. For example, the 2003 MRC report included an insightful comparison of UK research findings with related studies conducted in other nations involved in the 1991 Gulf War: they noted, 'There is a notably similar pattern of findings irrespective of where Gulf War veterans came from, or what their Gulf service experiences were. Gulf War veterans from several coalition countries consistently report suffering from more symptoms than non-Gulf War veterans, and these symptoms are similar despite markedly different exposures to vaccination, nerve agent pretreatments, oil fire smoke and other potential hazards.' Their bottom line conclusion, consistent with findings from the IOM, is that '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.'

Other committees (and date of publications) include:

- (i) Armed Forces Epidemiological Board (1996, 1999, 2000a,b), US Department of Defense (1999).
- (ii) Goss Gilroy Inc. Canadian epidemiological study of Gulf War veterans (1998a).
- (iii) The Rt Hon The Lord Lloyd of Berwick. Independent public inquiry on gulf war illnesses (2004).
- (iv) US Department of Veterans Affairs, Research Advisory Committee on Gulf War Veterans Illnesses, James Binns, Chair. Scientific progress in understanding Gulf War veterans' illnesses: report and recommendations (2004a,b).
- (v) US Department of Defense Special Oversight Board for Department of Defense Investigations of Gulf War Chemical and Biological Incidents. Final Report (2000).
- (vi) US Department of Defense. Report of the Defense Science Board Task Force on Persian Gulf War health effects (1994).
- (vii) US Department of Health & Human Services, National Institutes of Health Technology

Table 2. 1991 Gulf War hazardous agents, defined in law by US Congress in Public Laws 102-277 and 102-368, to be evaluated by the National Academy of Sciences Institute of Medicine.

chlorpyrifos
dichlorvos
propxur
methomyl
lindane
permethrins
DEET
tabun
hydrazine
solvents
microwave radiation
hydrogen sulphide
diesel heater fumes
diseases endemic to the region including leishmaniasis, sandfly fever, pathogenic <i>Escherichia coli</i> and shigellosis
diazinon
malathion
carbaryl
pyridostigmine bromide
pyrethrins
rodenticides
sarin
mustard agents, at levels below those which cause immediate blistering
red fuming nitric acid
depleted uranium
radio frequency radiation
oil fire byproducts
sand micro-particles
time-compressed administration of multiple live, 'attenuated' and toxoid vaccines

Assessment Workshop Panel. The Persian Gulf experience and health (1994)

- (viii) US Government Accountability Office (GAO). Gulf War illnesses: DOD's conclusions about US troops' exposure cannot be adequately supported (2004).
- (ix) US Presidential Advisory Committee on Gulf War veterans' illnesses: interim report (1996a).
- (x) US Presidential Advisory Committee on Gulf War veterans' illnesses: final report (1996b).
- (xi) US Presidential Advisory Committee on Gulf War veterans' illnesses: special report (1997).
- (xii) United Kingdom Parliamentary Office of Science and Technology. Gulf war illnesses: dealing with the uncertainties (1997).
- (xiii) United States Senate, Committee on Veterans' Affairs, Report of the special investigation unit on Gulf War illnesses (1998).

(c) *Congressionally mandated studies on Gulf War veterans' health*

Recognizing the IOM's potential contribution, in 1998, Congress directed in two statutes (Public Laws 105-277 and 105-368) that VA request the IOM to conduct reviews of the scientific and medical literature on the long-term health effects from exposure to a wide range of environmental hazards related to the 1991 Gulf War. Congress modelled these statutes after the earlier Agent Orange Act of 1991 described earlier, which established a similar review process to evaluate possible health

effects among Vietnam veterans from exposure to Agent Orange, other herbicides and their impurities. The two statutes also listed nearly three dozen different specific environmental exposures or categories of exposures of concern (table 2). Congress directed the NAS-IOM to 'identify the biological, chemical, or other toxic agents, environmental or wartime hazards, or preventive medicines or vaccines to which members of the Armed Forces who served in the Southwest Asia theatre of operations during the Persian Gulf War may have been exposed by reason of such service.'

Based on these statutes, the IOM has produced three major reports and one update for VA on health effects from a variety of hazardous exposures associated with the 1991 Gulf War (table 3).

(d) *Evidence categories*

The IOM has established a standardized method for rating the quality of published scientific and medical evidence associating a specific environmental hazard to a specific illness or disease among veterans. These are essentially identical to those used to evaluate Agent Orange health effects.

Their default category of association is 'inadequate/insufficient evidence to determine whether an association exists.' That is, an IOM committee begins with a neutral assumption that the 'evidence is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between exposure to a specific agent and a specific health outcome in humans.' Of course, the purpose of the IOM review is to search for evidence that can change this default. They have three categories for a positive association between an environmental hazard and health effect: (1) 'sufficient evidence of an association,' (2) 'sufficient evidence of a causal association' and the weakest positive category (3) 'limited/suggestive evidence of an association.' There is also one category for a negative association as 'limited/suggestive evidence of no association.'

It is important to note that a possible association between a specific hazard and health outcome may remain in the default category of 'insufficient/inadequate evidence of an association' either because (i) there is simply too little evidence to evaluate, or (ii) because a substantial body of evidence does not allow any more definitive conclusion.

3. IOM COMMITTEE CONCLUSIONS ON GULF WAR HEALTH RISK FACTORS

Four IOM committees have produced thorough reviews of relevant scientific and medical literature on virtually all of the popularized Gulf War environmental health concerns, summarized in table 4. This exhaustive process over 7 years involved review of thousands of scientific articles, and their results are also briefly summarized below.

Overall, this exhaustive and systematic literature review process has served to codify our understanding of Gulf War risk factors, but because most of these risk factors have been previously well characterized and much of the research reports involved non-military populations, the process has added little to our understanding of Gulf War veterans' health issues. As with

Table 3. Peer-reviewed publications on 1991 Gulf War hazardous agents reviewed by four IOM 'Gulf War & Health' committees. (As this manuscript was in preparation, the IOM had begun major reviews on long-term health effects from deployment-related stress, infectious diseases associated with both the 1991 and current Gulf Wars, and on clinical treatment implications based on a review of the entire scientific literature on Gulf War veterans' health research. Completion of those studies is anticipated in 2006.)

IOM report year	1991 Gulf War hazardous agent reviewed	peer-reviewed publications examined
2000	depleted uranium pyridostigmine bromide sarin selected vaccines including for anthrax and botulinum toxin	the IOM committee reviewed more than 10 000 abstracts of scientific and medical articles and then carefully examined the full text of over 1000 peer-reviewed journal articles
2003	pesticides and solvents used in the 1991 Gulf War	an initial literature search retrieved about 30 000 articles, which the IOM committee narrowed down to about 3000 peer-reviewed studies that the committee carefully reviewed
2004	sarin (update on literature published since 2000, the date of the first review on sarin)	a literature search retrieved about 250 titles published after the 2003 review, and the committee carefully reviewed all potentially relevant studies
2005	fuels, combustion products (primarily from oil-well fires) and propellants (primarily red fuming nitric acid and hydrazines)	an extensive search of the epidemiologic literature retrieved over 33 000 potentially relevant references; after assessing these, the committee focused on about 800 for careful review and evaluation

most of its studies, IOM committees focused on peer-reviewed published literature to form conclusions.

Their initial 2000, 600-page IOM report reviewed all peer-reviewed literature on health effects from DU, pyridostigmine bromide (PB), sarin and certain vaccines, and reached the following conclusions.

(a) *Depleted uranium*

DU, a by-product of the uranium enrichment process, is a low-level radioactive element as well as a heavy metal. About 340 tons of DU were used in munitions during the 1991 Gulf War. Used for both vehicle armour and armour-piercing munitions, DU primarily emits alpha radiation, which has a very short range and little penetrating power, making it hazardous only when in close proximity to tissue, e.g. via ingestion or inhalation. Uranium is also considered to have toxicity as a heavy metal, with the kidney as the vulnerable organ. DU munitions may release significant amounts of DU particles in various forms upon impact, which may be inhaled. DU munitions also produce fragments that leave DU shrapnel in wounds. Exposure to DU during the 1991 Gulf War could have occurred from 'friendly fire' incidents, cleanup operations and accidents, via inhalation and ingestion of particles and retention of DU shrapnel. Long-term health effects from such exposures have led to significant public controversy in the United Kingdom and the United States. The topic of DU exposure and health is considered in more detail elsewhere in [Squibb & McDiarmid \(2006\)](#)

The IOM committee focused primarily on 12 epidemiological studies of uranium processing workers (milling and processing uranium primarily for nuclear weapons and nuclear reactors; [table 5](#)). Most were mortality studies of uranium millers, and workers at uranium enrichment facilities, nuclear fuel fabricators and workers in a phosphate fertilizer plant (processing phosphate ore can result in uranium exposure). Exposure of uranium millers came primarily from dust inhalation, the most relevant route for exposed Gulf War veterans. Many of the workers evaluated in these

occupational studies would have experienced nearly daily exposures over much of their working lifetime, and adjustment for cigarette smoking was a common problem. Studies of miners were also examined but were considered less relevant as they focused primarily on radon health effects.

Based upon their analysis of these studies the IOM committee reached three major conclusions regarding the association between exposure to DU and illnesses.

- (i) *Lung cancer*. The committee concluded that there is limited/suggestive evidence of *no* association between exposure to uranium at cumulative internal dose levels lower than 200 mSv or 25 cGy. However, they reported inadequate/insufficient evidence to determine whether an association does or does not exist between exposure to uranium and lung cancer at higher levels of cumulative exposure.
- (ii) *Renal function*. They concluded that there is limited/suggestive evidence of *no* association between exposure to uranium and clinically significant renal dysfunction. That is, the kidney does not appear to be a significant target in humans exposed to uranium.
- (iii) *Other health outcomes*. The committee concluded that there is inadequate/insufficient evidence to determine whether an association does or does not exist between exposure to uranium and the following health outcomes: lymphatic cancer; bone cancer; nervous system disease; non-malignant respiratory disease; or other health outcomes (gastrointestinal disease, immune-mediated disease, effects on haematological parameters, reproductive or developmental dysfunction, genotoxic effects, cardiovascular effects, hepatic disease, dermal effects, ocular effects and musculoskeletal effects).

At about the same time, in the United Kingdom, the Royal Society responded by convening an independent expert working group, under the chairmanship of

Table 4. Summary of IOM 'Gulf War & Health' committee findings on health effects from environmental hazards associated with the 1991 Gulf War, by category of evidence (IOM report volume in parenthesis). (ct, cohort study; cc, case-control study; cs, case-series; epi, epidemiological; long, longitudinal; occu, occupational; pop, population.)

	selected epidemiological and other studies
<p><i>Evidence category 1: 'sufficient evidence of a causal relationship'</i> 'evidence is sufficient to conclude that there is a causal association between exposure to a specific agent and a specific health outcome in humans; the evidence is supported by experimental data and fulfils the guidelines for sufficient evidence of an association (below); the evidence must be biologically plausible and satisfy several of the guidelines used to assess causality, such as: strength of association, dose-response relationship, consistency of association and a temporal relationship'</p>	
1. Cancers	8 occu ct and cc studies (acute leukaemia); 3 worker ct studies (aplastic anaemia)
benzene and acute leukaemia; and aplastic anaemia (2)	
2. Neurological effects	4 reviews on sarin toxicity
exposure to sarin and a dose-dependent acute cholinergic syndrome that is evident seconds to hours subsequent to sarin exposure and resolves in days to months (1 and 2004 update)	
<p><i>Evidence category 2: sufficient evidence of an association</i> 'evidence is sufficient to conclude that there is a positive association; i.e. a consistent positive association has been observed between exposure to a specific agent and a specific health outcome in human studies in which chance and bias, including confounding, could be ruled out with reasonable confidence; e.g. several high-quality studies report consistent positive associations, and the studies are sufficiently free of bias, including adequate control for confounding'</p>	
1. Cancers	10 occu ct mortality studies 5 occu and other cc studies 82 epi studies including ct studies on ambient air pollution, occu studies for motor vehicle exhaust, cc studies of lung cancer patients
benzene and adult leukaemia (2) solvents and acute leukaemia (2) combustion products and lung cancer (3)	approximately 180 references of animal studies, and clinical and epi studies including of Gulf War veterans 1 randomized clinical trial and four reports of acute adverse reactions in among vaccine recipients 2 peer-reviewed studies of laboratory workers receiving the vaccine 4 occu studies
2. Neurological and other health effects	
pyridostigmine bromide and transient acute cholinergic effects in doses normally used in treatment and for diagnostic purposes (1) anthrax vaccination and transient acute local and systemic effects (1) botulinum toxoid vaccination and transient acute local and systemic effects (1) propylene glycol and allergic contact dermatitis (2)	
<p><i>Evidence category 3: limited/suggestive evidence of an association</i> 'evidence is suggestive of an association between exposure to a specific agent and a specific health outcome, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence; e.g. at least one high-quality study reports a positive association that is sufficiently free of bias, including adequate control for confounding; other corroborating studies provide support for the association, but they were not sufficiently free of bias, including confounding; alternatively, several studies of lower quality show consistent positive associations, and the results are probably not due to bias, including confounding'</p>	
1. Cancers	8 (bladder) and 11 (kidney) occu ct and cc studies 22 (multiple myeloma), 42 adult leukaemia, 9 myelodysplastic syndromes and 42 bladder cancer occu cc and ct studies 13 cc (non-Hodgkin's) and 9 cc and ct studies (adult leukaemia) 8 cc studies 16 occu ct and cc studies
tetrachloroethylene and dry-cleaning solvents and bladder and kidney cancer (2) solvents and multiple myeloma, adult leukaemia, myelodysplastic syndromes and bladder cancer (2) organophosphorus insecticides and non-Hodgkin's lymphoma and adult leukaemia (2) carbamates and non-Hodgkin's lymphoma (2) benzene and non-Hodgkin's lymphoma (2)	

(Continued.)

Table 4. (Continued.)

selected epidemiological and other studies	
combustion products and cancers of the nasal cavity and nasopharynx; cancers of the oral cavity and oropharynx; laryngeal cancer; and bladder cancer (3)	4 epi occup and other cc studies (nasal cavity and nasopharynx), 9 occup and ambient pollution cc studies (oral cavity and oropharynx), 17 ct and cc occup studies (laryngeal) and 17 occup cc and ct studies (bladder)
hydrazines and lung cancer (3)	5 ct studies of workers employed for 2 years or more at a rocket testing facility, at a hydrazine production facility and 3 cs studies of rocket fuel handlers and manufacturers
2. Neurological and other health effects	
exposure to sarin at doses sufficient to cause acute cholinergic signs and symptoms and subsequent long-term health effects (1 and 2004 update)	42 studies (see tables 6–8) of Gulf War veterans and of results of occup exposures, accidents and military human experiments
organophosphorus insecticide exposure with OP poisoning and long-term neurobehavioural effects (i.e. abnormal results on neurobehavioural test batteries and symptom findings) (2)	4 occup ct studies
solvents and neurobehavioural effects (i.e. abnormal results on neurobehavioural test batteries and symptom findings) (2)	7 occup and twin studies
solvents and reactive airways dysfunction syndrome (RADS) which would be evident with exposure and could persist for months or years (2)	15 clinical and epi occup studies
solvents and hepatic steatosis and chronic glomerulonephritis (2)	8 occup case reports, series, clinical and epi studies
insecticides and allergic contact dermatitis (2)	2 controlled studies of farmers
3. Reproductive effects	
combustion products and low birthweight/intrauterine growth retardation and exposure during pregnancy (3)	8 epi studies of pregnant women exposed to ambient air pollution
preterm birth and exposure during pregnancy (3)	4 epi studies of women exposed to air pollutants
<i>Evidence category 4: inadequate/insufficient evidence of an association</i>	
'evidence is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between exposure to a specific agent and a specific health outcome in humans'	
1. Cancers and other health effects	
exposure to uranium and lung cancer at higher levels of cumulative exposure (greater than 200 mSv or 25 cGy) (1)	12 epi occup mortality and morbidity studies (see table 5)
exposure to uranium and lymphatic cancer; bone cancer; nervous system disease; non-malignant respiratory disease; or other health outcomes (gastrointestinal disease, immune-mediated disease, effects on haematological parameters, reproductive or development dysfunction, genotoxic effects, cardiovascular effects, hepatic disease, dermal effects, ocular effects, or musculoskeletal effects) (1)	12 epi occup mortality and morbidity studies (see table 5)
solvents and oral, nasal, or laryngeal cancer; ovarian or uterine cancer; prostate cancer; bone cancer; melanoma or non-melanoma skin cancer; and stomach, rectal, or pancreatic cancer (2)	few inadequate studies to evaluate association for oral, nasal, or laryngeal cancer; ovarian or uterine cancers. 26 occup studies (prostate), 4 (bone), 15 (melanoma), 9 (non-melanoma), 28 (stomach), 20 (rectal) or 24 (pancreatic cancers) showed no consistent association
solvents other than tetrachloroethylene and dry-cleaning solvents and oesophageal cancer; cervical cancer; and lung cancer (2)	13 occup studies (oesophageal), 9 (cervical), and 40 (lung cancer) studies showed no consistent association
solvents other than trichloroethylene and mixtures of benzene, toluene and xylene and colon cancer (2)	9 occup studies showed no consistent association
solvents other than benzene and aplastic anaemia (2)	3 cc studies showed no consistent association

(Continued.)

Table 4. (Continued.)

selected epidemiological and other studies	
specific solvents other than benzene and acute and adult leukaemia (2) benzene and myelodysplastic syndromes (2) insecticides and pancreatic cancer; lung cancer; prostate, testicular, bladder, or kidney cancers; soft tissue sarcomas; brain and other central nervous system cancers; and aplastic anaemia (2) lindane or solvents and breast cancer (2)	32 (adult leukaemia) and 5 (acute leukaemia) occup studies showed no consistent association 1 ct occup study was inadequate 2 cc (pancreatic), 5 occup (lung), 1 occup (prostate), 2 cc and ct study (testicular), 1 cc (kidney), 1 cc (soft tissue sarcoma), 4 ct and cc (brain), and 4 cc studies (aplastic anaemia) provided inadequate evidence of an association 5 cc (lindane) and 24 primarily occup (solvents) studies provided inadequate evidence of an association
specific solvents other than tetrachloroethylene and dry-cleaning solvents and bladder cancer; and kidney cancer (2) specific solvents other than benzene and brain and other central nervous system cancers; and non-Hodgkin's lymphoma (2) insecticides and solvents and Hodgkin's disease; and hepatobiliary cancers (2)	34 (bladder) and 39 (kidney) primarily occup studies provided inadequate evidence of an association 29 (brain) and 55 (non-Hodgkin's) occup and other studies provided inadequate evidence of an association 1 cc (insecticides and Hodgkin's), 4 cc (insecticides and Hodgkin's), 27 cc and ct occup (solvents and Hodgkin's), 33 ct occup (solvents and hepatobiliary), and 3 cc and ct occup studies (insecticides and hepatobiliary cancers) provided inadequate evidence of an association
insecticides and specific solvents and multiple myeloma (2)	22 ct and cc occup (solvents), and 5 cc (insecticides) studies provided inadequate evidence of an association
fuels and cancers of the oral cavity and oropharynx; cancers of the nasal cavity and nasopharynx; oesophageal cancer; stomach cancer; colon cancer; rectal cancer; hepatic cancer; pancreatic cancer; laryngeal cancer; lung cancer; melanoma; non-melanoma skin cancer; female and male breast cancer; female genital cancers (cervical, endometrial, uterine, and ovarian cancers); prostate cancer; testicular cancer; nervous system cancers; kidney cancer; bladder cancer; Hodgkin's disease; non-Hodgkin's lymphoma; multiple myeloma; and myelodysplastic syndromes (3)	5 ct and cc occup (oral cavity and oropharynx); 2 cc (nasal cavity and nasopharynx); 3 occup ct (oesophageal); 5 occup ct and cc (stomach); 6 occup ct and cc (colon); 6 occup ct and cc (rectal); 1 occup cc (hepatic); 2 occup cc (pancreatic); 5 occup ct and cc (laryngeal); 3 occup ct and cc (lung); 5 occup ct (melanoma); 3 occup ct and cc (non-melanoma skin); 4 occup ct and cc studies (female and male breast); 3 occup ct and cc (female genital); 3 occup ct and cc (prostate); 6 occup ct and cc (nervous system); 14 occup cc (bladder); 14 occup ct and cc (kidney); 9 occup ct and cc (non-Hodgkin's); 6 occup ct (Hodgkin's); 11 occup ct and cc (multiple myeloma); 3 occup cc (myelodysplastic syndromes) 5 occup ct and cc (oesophageal); 6 occup ct and cc (stomach); 3 occup cc (colon); 3 occup cc (rectal); 1 cc (hepatic); 3 occup cc (pancreatic); 8 occup ct and cc (melanoma); 4 occup cc (female and male breast); 3 occup cc (female genital); 4 occup cc (prostate); 2 occup cc (nervous system); 3 occup cc (ocular melanoma) 8 occup ct and cc (kidney); 6 occup ct and cc (non-Hodgkin's); 3 occup ct and cc (Hodgkin's); 10 occup cc (multiple myeloma); 6 occup ct and cc (leukaemias); and 2 occup cc (myelodysplastic syndromes)
combustion products and oesophageal cancer; stomach cancer; colon cancer; rectal cancer; hepatic cancer; pancreatic cancer; melanoma; female and male breast cancer; female genital cancers (cervical, endometrial, uterine and ovarian cancers); prostate cancer; testicular cancer; nervous system cancers; ocular melanoma; kidney cancer; non-Hodgkin's lymphoma; Hodgkin's disease; multiple myeloma; leukaemia; and myelodysplastic syndromes (3) hydrazines and haematopoietic and lymphopoietic cancers; digestive tract cancers; pancreatic cancer; bladder cancer; and kidney cancer (3) nitric acid and stomach cancer; melanoma; lymphopoietic cancers; pancreatic cancer; laryngeal cancer; lung cancer; bladder cancer; and multiple myeloma (3)	1 occup ct (lymphopoietic); 1 occup ct (digestive tract); 1 occup ct (pancreatic); and 1 occup ct (bladder and kidney) 2 occup ct (lymphopoietic); 7 occup ct and cc (laryngeal); 6 occup ct (lung); and 1 occup cc (multiple myeloma)

2. Neurological and other health effects

pyridostigmine bromide and long-term adverse health effects (1)
exposure to sarin at low doses insufficient to cause acute cholinergic signs and symptoms
and subsequent long-term adverse health effects (1 and 2004 update)
exposure to sarin and subsequent long-term cardiovascular effects (2004 update)
anthrax vaccination and long-term adverse health effects (1)

numerous negative epi and clinical studies; 2 surveys of Gulf War veterans
34 studies (see tables 6-8)

(see tables 7 and 8)

1 randomized peer-reviewed study

(Continued.)

Table 4. (Continued.)

selected epidemiological and other studies	
botulinum toxoid vaccination and long-term adverse health effects (1) multiple vaccinations and long-term adverse health effects (1) solvents and multiple sclerosis; a long-term reduction in colour discrimination; long-term hearing loss; long-term reduction in olfactory function; cirrhosis; alterations in liver function tests after cessation of exposure; chronic pancreatitis and other persistent gastrointestinal outcomes; and the systemic rheumatic diseases: scleroderma, rheumatoid arthritis, undifferentiated connective tissue disorders, and systemic lupus erythematosus (2) insecticides and solvents and peripheral neuropathy; Parkinson's disease; amyotrophic lateral sclerosis; Alzheimer's disease; irreversible cardiovascular outcomes; and persistent respiratory symptoms or impairment after cessation of exposure (2)	no long-term human studies available 3 limited occup studies 4 occup cc (multiple sclerosis); 1 occup long and several cs (long-term reduction in colour discrimination); 3 long and other occup (hearing loss); 3 occup cs (olfactory function); 5 limited occup (cirrhosis); 12 occup (liver function); 1 occup cc (pancreatitis); and 7 occup cc (systemic rheumatic diseases)
combustion products and neurobehavioural effects; PTSD; nervous systems or individual nervous system diseases; multiple chemical sensitivity symptoms; respiratory effects including chronic bronchitis (with less than 1 year of exposure); emphysema; chronic obstructive pulmonary disease; and ischaemic heart disease or myocardial infarction (with less than 2 years of exposure; dermatitis—irritant and allergic; and sarcoidosis (3) fuels and peripheral neuropathy; neurobehavioural effects; multiple chemical sensitivity symptoms; respiratory effects including non-malignant respiratory disease; chronic bronchitis; asthma; emphysema; dermatitis—irritant and allergic; and sarcoidosis (3) hydrazines and ischaemic heart disease or myocardial infarction; and hepatic diseases (3) nitric acid and cardiovascular disease (3)	5 occup (solvents and peripheral neuropathy); 3 Gulf War veteran (including pesticides and peripheral neuropathy); 2 cc (solvents and peripheral neuropathy); 6 cc (insecticides and peripheral neuropathy); 6 occup or high exposure cc (insecticides and PD); 2 occup cc (solvents and PD); 5 cc (pesticides and ALS); 4 cc (solvents and ALS); 2 cc (insecticides and Alzheimer's); and 5 occup cc (Alzheimer's and solvents) 6 occup (PTSD); 4 ct (neurologic disease); 2 occup cs (neurobehavioural); numerous occup and Gulf War veteran studies (respiratory effects and cardiovascular disease); and 3 occup cc (sarcoidosis)
3. Reproductive effects	
insecticides and solvents and male or female infertility after cessation of exposure (2) parental preconception exposure to insecticides or solvents and spontaneous abortion or other adverse pregnancy outcomes; and congenital malformations (2) parental preconception exposure to insecticides and childhood leukaemias, brain and other central nervous system cancers, and non-Hodgkin's lymphoma (2) parental preconception exposure to solvents and neuroblastoma, childhood leukaemia, and childhood brain cancers (2) fuels and adverse reproductive or developmental outcomes (including infertility, spontaneous abortion, childhood leukaemia, CNS tumours, neuroblastoma, and Prader-Willi syndrome (3) combustion products and preterm births and exposure during any specific time period during pregnancy (for example, the first trimester); low birth weight and intrauterine growth retardation and exposure before gestation or during any specific period during pregnancy (for example, the first trimester); specific birth defects including cardiac effects, and exposure before conception (maternal and paternal) or during early pregnancy (maternal); and all childhood cancers identified including acute lymphocytic leukaemia, leukaemia, neuroblastoma, and brain cancer (3)	2 occup cs (peripheral neuropathy); 1 cc (neurobehavioural effects); 21 occup cs (respiratory effects including non-malignant respiratory disease; chronic bronchitis; asthma; emphysema); and 4 occup cc (dermatitis) 1 occup ct (ischaemic heart disease) 2 occup ct 3 occup epi (insecticides and infertility); and 5 occup epi (solvents and infertility) 3 occup epi (solvents and spontaneous abortion); 6 occup epi (insecticides and congenital malformations); and 4 occup epi (solvents and congenital malformations) 2 pop cc (childhood leukaemia); 2 epi cc (brain cancers); and 1 ep cc (non-Hodgkin's) 2 occup cc (neuroblastoma); 6 occup ct and cc (childhood leukaemia); 2 occup cc (childhood brain) 1 limited occup epi (infertility); 1 limited pop epi (spontaneous abortion); 2 occup cc (leukaemias); 2 occup cc (neuroblastoma); 1 occup cc Prader-Willi); 4 pop ct (preterm births); 8 pop ct (low birthweight); 6 pop and occup ct (birth defects); 8 occup and pop ct and cc (childhood cancers)

(Continued.)

Table 4. (Continued.)

selected epidemiological and other studies	Evidence category 5: limited/suggestive evidence of no association 'evidence is consistent in not showing a positive association between exposure to a specific agent and a specific health outcome after exposure of any magnitude; a conclusion of no association is inevitably limited to the conditions, magnitudes of exposure, and length of observation in the available studies; the possibility of a very small increase in risk after exposure studied cannot be excluded'	
1. Cancer and other	exposure to uranium and lung cancer at cumulative internal dose levels lower than 200 mSv	12 epi studies (see table 5)
or 25 cGy (1)	exposure to uranium and clinically significant renal dysfunction (1)	12 epi studies (see table 5)

Sir Brian Heap, to review scientific literature on long-term health effects from DU exposure. That expert committee also was charged with considering whether exposure to DU could be a cause of the ill health seen in UK service personnel.

The two Royal Society 'working group' reports and one summary on DU reviewed the very extensive relevant published epidemiologic and animal research (The Royal Society 2001, 2002a,b). Like the IOM committee, they concentrated upon peer-reviewed materials. Their reports were reviewed and endorsed by the Council of the Royal Society. The working group also heard from a broad range of stakeholders with an interest in DU and its potential consequences.

Using broadly similar approaches, the Royal Society working group reached similar conclusions to those of the IOM committee on this issue. However, the Royal Society took the additional step of attempting to estimate actual DU exposure and the corresponding radiological and toxicological health risks experienced by veterans. As with essentially all risk factors associated with the 1991 Gulf War, little or no actual measurements are available of DU exposure, and exposure therefore must be estimated. The Royal Society estimated battlefield exposure levels based upon a range of scenarios, including a worst-case scenario considered as 'as not likely to have been exceeded.' They concluded that regardless of uncertainties, they could establish reasonable upper and lower limits on battlefield DU exposure and the subsequent health effects from that exposure.

Based on this approach, the expert working group concluded that the greatest risk from DU inhaled on the battlefield related to radiation was an increase in lung cancer risk (The Royal Society 2001, 2002b). Estimated average risk of other cancers, including leukaemia, were lower than those for lung cancer for all DU exposure scenarios. Under worst-case exposure estimates, excess lung cancer risk 'could be about one in 15.' For a large exposure, such as surviving in a tank struck with a DU munition, the working group estimated an average excess lung cancer risk of about one in a thousand. For smaller exposure, the excess lung cancer risk was about one in 40 000, or less. These figures compare to lifetime general population lung cancer risk of about one in 250 for non-smokers and one in six for cigarette smokers.

For toxicological health effects, the working group noted that the few human studies involving large uranium exposure result in limited information about serious adverse effects in kidney, the likely target organ in humans. 'Very few humans have had sufficiently large acute intakes of uranium compounds to lead to severe kidney dysfunction or kidney failure. Studies of these few cases indicate that kidney failure is likely to occur within a few days at concentrations above about 50 µg uranium per gram kidney.'

Based on these observations and estimated battlefield DU exposures, the working group concluded that 'it is not expected that adverse effects on the kidney would occur. Levels of uranium in the kidney of soldiers surviving in tanks struck by DU rounds, or of soldiers working for protracted periods in heavily contaminated vehicles, could lead to some short-term kidney dysfunction, but whether this would lead to any long-term

Table 5. Epidemiologic studies of uranium processing workers: from IOM's report 'Gulf War & Health: volume 1. Depleted uranium, pyridostigmine bromide, sarin, and vaccines,' 2000.

reference	study design	description	radiation dose in exposed subjects	study group (n)
Wagoner <i>et al.</i> (1964)	cohort	prospective cohort study of mortality experience of white male uranium millers and miners in the Colorado Plateau states	not known	611 millers
Archer <i>et al.</i> (1973)	cohort	prospective cohort study of mortality experience of white male uranium millers in the Colorado Plateau states	not known	662
Polednak & Frome (1981)	cohort	mortality experience of white male employees (1943–1947) at a uranium conversion and enrichment plant in Oak Ridge, TN	not known	18 869
Hadjimichael <i>et al.</i> (1983)	cohort	mortality and cancer incidence experience of employees (1956–1978) in a nuclear fuel fabrication plant in Connecticut	0.5% had greater than or equal to 10 rem cumulative dose ^a	4106
Waxweiler <i>et al.</i> (1983)	cohort	mortality experience of male uranium millers in the Colorado Plateau states	not known	2002
Stayner <i>et al.</i> (1985)	cohort	mortality experience of workers at a phosphate fertilizer production facility in Florida	not known	3199
Brown & Bloom (1987)	cohort	mortality experience of white male uranium enrichment workers in Ohio	not known	5773
Dupree <i>et al.</i> (1987)	cohort	mortality experience of white male employees of a uranium processing facility in Buffalo, NY	37.9% had greater than 10 rem per year estimated dose of internal radiation to the lung ^b	995
Checkoway <i>et al.</i> (1988)	cohort	mortality experience of white male employees (1947–1979) at a nuclear materials fabrication plant, in Oak Ridge, TN	29% had greater than or equal to 10 rem cumulative internal radiation dose ^c	6781
Frome <i>et al.</i> (1990)	cohort	mortality experience of white male workers at Oak Ridge uranium enrichment and laboratory facilities	not known	28 008
Dupree <i>et al.</i> (1995)	case control	cases of lung cancer at four uranium processing operations	5% of cases had greater than or equal to 0.5 cGy cumulative internal radiation dose	787
Ritz (1999)	cohort	mortality experience of white male employees at a uranium processing plant in Ohio	8.2% had greater than or equal to 10 rem internal radiation dose ^b	4014

^a Percentage of those with known exposure (of the total cohort of 4106 individuals, exposure was known for 786 individuals; four individuals had greater than or equal to 10 rem).

^b Data in the study were given in units of millisieverts and have been converted to rems.

^c Percentage of those with known exposure (of the total cohort of 6781 individuals, exposure was known for 3490).

adverse effects is unclear. According to worst-case assumptions, kidney uranium levels in some soldiers could be very high, and would probably lead to kidney failure within a few days of exposure, although we are unaware of any such cases of kidney failure' (The Royal Society 2002a).

Using their battlefield DU exposure estimates and review of relevant scientific and medical literature, the working group reached the following main conclusions about the increased risk to veterans of the 1991 Gulf War:

- (i) Except in extreme circumstances, any extra risks of developing fatal cancers as a result of radiation from internal exposure to DU arising from battlefield conditions are likely to be undetectable above the general risk of dying from cancer over a normal lifetime. This remains true even if the estimates of risk resulting from likely exposures are one hundred

times too low.

- (ii) The extreme circumstances will apply only to a very small fraction of the soldiers in a theatre of war, for example those who survive in a vehicle struck by a DU penetrator, or those involved in cleaning up struck vehicles. In such circumstances, and assuming the most unfavourable conditions, the lifetime risk of death from lung cancer could be about twice that in the general population.
- (iii) Any extra risks of death from leukaemia, or other cancers, as a result of exposure to DU are estimated to be substantially lower than the risks of death from lung cancer. Under all likely exposure scenarios, the extra lifetime risks of fatal leukaemia are predicted to be too small to be observable.
- (iv) Many soldiers on a battlefield may be exposed to small amounts of DU and the risks of cancer from such exposures are predicted to be very

low. Even if the estimates of risk for these conditions are one hundred times too low, it is unlikely that any excess of fatal cancer would be detected within a cohort of 10 000 soldiers followed over 50 years.

- (v) The radiological risks from the use of DU in munitions are for the most part low, but there are uncertainties in the levels of exposure that could occur under unfavourable conditions, and for small numbers of soldiers there could be circumstances in which the excess risks of lung cancer are substantial. Therefore, they recommended that further work be undertaken to clarify the extent of intakes on the battlefield.
- (vi) The estimated DU intakes for most soldiers on the battlefield are not expected to result in concentrations of DU in the kidney that exceed 0.1 µg per gram of kidney, even transiently. Consequently, in these cases, it is not expected that adverse effects on the kidney or any other organ would occur.
- (vii) Levels of uranium in the kidney of soldiers surviving in tanks struck by DU rounds, or of soldiers working for protracted periods in heavily contaminated vehicles, could reach concentrations that lead to some short-term kidney dysfunction, but whether this would lead to any long-term adverse effects is unclear as adequate studies of the long-term effects on the kidney of acute or protracted exposures to elevated levels of uranium are not available. According to worst-case assumptions, kidney uranium levels in some soldiers could be very high, and would probably lead to kidney failure within a few days of exposure. However, they were not aware of any cases of kidney failure, occurring within a few days of exposure, in US soldiers who would have received the highest DU intakes during the Gulf War, but they could not rule out some kidney damage for such soldiers under worst-case assumptions.
- (viii) For those returning to live in areas where DU munitions were deployed, including peace-keepers, the inhalation intakes from re-suspended DU are considered to be unlikely to cause any substantial increase in lung cancer or any other cancers. The estimated excess lifetime risk of fatal lung cancer is about one in a million, although there could be higher risks for some individuals with worst-case intakes of DU due to higher levels of local contamination. Estimated risks of other cancers are at least 100-fold lower. There are, however, large uncertainties in the estimates of inhalation intakes in the years following a conflict.
- (ix) No effects on kidney function from inhalation of re-suspended DU are expected for most individuals who return after a conflict. Small effects on kidney function are possible using worst-case assumptions, but would at most only apply to a small number of individuals.
- (x) Although there is no clear evidence that occupational exposures to uranium have consequences for reproductive health, effects on

reproductive health have been observed in mice after high intakes of uranium. Accordingly, epidemiological studies of the reproductive health of Gulf War veterans and of the Iraqi population are underway. If effects are seen, then further investigation would be required to determine the relative contributions from DU and from other possible causes.

Similarly, citing the Royal Society report, the 2003 MRC reported concluded that '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.'

(b) *Sarin*

Health concerns from exposure to low levels of sarin became a significant issue for veterans of the 1991 Gulf War following revelations that some Iraqi munitions destroyed by US forces at Khamisiyah, Iraq, after the March 1991 cease-fire contained this chemical warfare agent. To evaluate short- and long-term health effects from organophosphorus (OP) military and insecticidal nerve agents, reviewers including IOM committees and the MRC have an abundant scientific literature to consider. This literature, published over more than five decades, includes data from actual human experimentation, from occupational and accidental exposures, laboratory animals and from terrorist attacks including the 1994 and 1995 sarin attacks in Japan.

Four distinct health effects have been described, including (i) acute cholinergic toxicity, (ii) organophosphate-induced delayed neuropathy (OPIDN), (iii) subtle long-term neuropsychological and neurophysiological effects and (iv) a reversible muscular weakness known as 'intermediate syndrome.' Some effects described in this literature are subtle, often difficult to differentiate from health effects caused by other diseases or occupational exposures.

Consistent with general toxicological principles, each described health effect has data suggesting threshold exposure levels below which it is unlikely to be clinically detectable. Therefore, meaningful interpretation of human and animal studies requires strict characterization of the exposure.

Because precise exposure levels are often difficult to reconstruct, a system for characterizing exposure has been proposed based upon observed *initial* acute signs and symptoms, as high-level (definitive cholinergic poisoning); intermediate-level (threshold cholinergic effects including miosis, rhinorrhoea or clinically measurable depression of cholinesterase); and low-level (no immediate clinical signs or symptoms) exposure (Brown & Brix 1998).

A basic conclusion of reviews by the IOM and others is that there exist threshold or minimum exposure levels for all known long-term effects from OP nerve agent, and that those thresholds are at or above intermediate level exposure. Long-term health effects seen at intermediate-level exposures or in many survivors of high-level exposure are subtle, detectable in exposed populations but not individuals, and not reported in

Table 6. Sarin health effects studies used in IOM's report 'Gulf War & Health: volume 1. Depleted uranium, pyridostigmine bromide, sarin, and vaccines,' 2000.

sarin study reference	description
Baker & Sedgwick (1996)	8 male UK military volunteers exposed to sarin and developed acute poisoning, evaluated with electromyography
Burchfiel <i>et al.</i> (1976), Duffy <i>et al.</i> (1979), Burchfiel & Duffy (1982)	study of long-term CNS effects in 77 industrial workers with documented acute exposure to sarin in the 1950s and 1960s
Haley & Kurt (1997), Roland <i>et al.</i> (2000)	249 veterans from a naval battalion who believed themselves exposed to sarin during the Gulf War
Metcalf & Holmes (1969)	industrial workers exposed in the 1950s and 1960s
Morita <i>et al.</i> (1995)	155 residents who were victims of the sarin terrorist attacks in Matsumoto City in 1994 and Tokyo in 1995
Nakajima <i>et al.</i> (1998), Nakajima <i>et al.</i> (1999)	population-based study of long-term effects among a group of about 600 victims and 2000 residents near the Matsumoto City sarin terrorist attack
NRC (1982), NRC (1985)	military volunteers experimentally exposed between 1958 and 1975 to non-lethal doses of sarin and other chemical warfare agents
Ohbu <i>et al.</i> (1997)	survey at 1, 3 and 6 months of 610 victims of the Tokyo sarin terrorist attack
Sekijima <i>et al.</i> (1997)	follow up of severely acutely poisoned victims of the Matsumoto City terrorist sarin attacks
Murata <i>et al.</i> (1997), Yokoyama <i>et al.</i> (1998a-c)	18 survivors of the Tokyo sarin terrorist attack evaluated for CNS and other neurobehavioural and neuropsychological effects six to eight months later

individuals experiencing low-level exposure alone. From a practical perspective, this means that long-term health effects from these agents are seen only in the aftermath of acute clinical poisoning, or to put it another way, such long-term effects are unlikely in the absence of evidence of acute signs and symptoms of poisoning.

Two IOM committees (2000 and 2004) reached several essentially identical conclusions about long-term health effects from sarin for different exposure levels, as defined by the magnitude of initial acute poisoning signs and symptoms. As the IOM committee pointed out, medical reports by the US Army Medical Corps at the time of the Khamisiyah incident were consistent with the absence of any acute sarin poisoning: 'US troops did not report acute cholinergic symptoms at the time, but the possibility of low-level, asymptomatic exposures cannot be discounted.' Therefore, the key health issue for veterans of the 1991 Gulf War was the possibility of long-term health effects following sub-clinical exposure to sarin, that is, following an exposure causing no acute poisoning signs and symptoms.

A 2003 UK MRC report also noted that subtle effects following acute OP poisoning have been reported, but that no evidence for these effects has been reported following low-level non-acute exposures. They concluded that, 'The evidence linking UK Gulf War veterans' illnesses to actual measures of nerve gas or OP pesticide exposure is extremely poor. There is no confirmed evidence that nerve gases 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 MRC report also considered whether some individuals might be uniquely sensitive to OP poisoning as a result of variations reported in the enzyme paraoxonase among some ill Gulf War veterans, which

break down these chemicals. However, the MRC concluded that the significance of these findings was not clear and would require further study.

The 2003 MRC report also concluded that although ill veterans of the 1991 Gulf War consistently report an unusually high level of neurological symptoms, clinical investigations had not uncovered significant evidence of malfunction in the peripheral nervous system or nerve/muscle junctions.

The IOM committee reviewed a number of human studies on sarin health effects, as well as a wide range of laboratory animal studies. They focused upon studies of four human populations exposed to sarin, including military volunteers in experiments conducted in the US and UK several decades ago involving exposure to sarin and other chemical warfare agents, industrial workers involved in the manufacture of sarin and victims of terrorist attacks in Matsumoto City and Tokyo, Japan, in 1994 and 1995 (table 6).

The 2000 IOM committee also reviewed the hypothesis that exposure to sub-clinical traces of sarin might produce a new, previously undescribed disease—a 'Gulf War Syndrome' (Haley & Kurt 1997). Supporters of this hypothesis presented evidence to the committee during an open two-day meeting 16 and 17 September 1999, in Washington, DC (appendix B, 'Gulf War and health: volume 1. Depleted uranium, pyridostigmine bromide, sarin, and vaccines.' National Academy Press, 2000). Nevertheless, the committee did not endorse this hypothesis, and, in fact, their most important conclusion relative to Gulf War health effects was that there was 'inadequate/insufficient evidence of an association' between exposure to sub-clinical levels of sarin and any subsequent long-term health effects.

Not surprisingly, considering the fact that these chemical agents are designed to kill or incapacitate, the committee also found 'sufficient evidence of a causal relationship' between exposure to sarin and a dose-dependent acute cholinergic syndrome that is evident seconds to hours subsequent to sarin exposure and resolves in days to months.

The IOM committee also reported 'limited/suggestive evidence of an association' between exposure to sarin at doses sufficient to cause acute cholinergic signs and symptoms and subsequent long-term health effects, based primarily on studies of three groups of people exposed to sarin: (i) workers occupationally exposed to sarin in the 1950s and 1960s; (ii) a terrorist attack on civilians in Matsumoto, Japan in 1994; and (iii) a terrorist attack on civilians in Tokyo, Japan in 1995. As previously described, no Gulf War veteran was known to have experienced an exposure this large, which caused acute symptomatic illness.

The committee pointed out that the Japanese survivors of terrorist attacks obviously experienced a wide range of exposures, as well as the stress of the event itself. Some terrorist victims showed severe cholinergic poisoning that required hospitalization or even resulted in death, some showed milder signs and symptoms, and some were exposed at levels leading to no acute effects. Commonly reported long-term health consequences including increased risk of PTSD and reports of 'fear of subways' are likely to have derived from the psychological stress of the terrorist attack rather than directly from cholinergic poisoning.

Perhaps host variation may explain differences in individual susceptibility. Haley has claimed that polymorphisms in the enzyme detoxification pathways for organophosphate compounds are related to symptoms (Haley *et al.* 1999), which is theoretically plausible (Furlong 2000), but has not been confirmed in two studies from the UK (Mackness *et al.* 2000; Hotopf 2003). Finally, animal experiments have failed to confirm any adverse delayed neurobehavioural effects or other significant effects from low-dose pyridostigmine alone or in combination with low-dose sarin, as well as confirming that pyridostigmine did convey some protection against sarin, the purpose for which it is administered (Scremin *et al.* 2003).

The IOM committee also addressed the issue of a possible unusual genetic susceptibility to sarin toxicity in humans, and reported that the data was equivocal. The enzyme paraoxonase (PON1) found in humans in the brain and the blood is an esterase involved in sarin detoxification. The IOM committee pointed out that the human *PON1* gene has polymorphisms at positions 192 (*Arg/Gln*) and 55 (*Leu/Met*) that affect serum PON1 activity (Furlong *et al.* 1993).

Because human serum PON1 catalyses the hydrolysis of OP insecticides and nerve gases such as sarin, those polymorphisms might substantially alter a person's susceptibility to the toxicity of the chemicals. The polymorphism at position 192 accounts for three genotypes (QQ, RR and QR) related to the catalytic properties of two forms of the PON1 enzyme (types R and Q allozymes), which hydrolyse some organophosphates at different rates.

The R allozyme (*Arg*₁₉₂) hydrolyses the organophosphate paraoxon at a high rate; however, it has a low activity against OP nerve agents, such as sarin and soman (Davies *et al.* 1996). Lower activity means that more sarin would be bioavailable to exert its anticholinesterase effects. The Q allozyme has high activity against OP nerve agents and low activity against paraoxon. Thus, people with the Q allozyme (genotype

QQ or QR) are expected to have greater hydrolysis of sarin than people homozygous for the R allele (genotype RR). Animal studies support the role of PON1 in protection against the toxicity of some OP compounds (Costa *et al.* 2003). The prevalence of the R allele is about 0.3 in Caucasian populations but 0.66 in the Japanese population (Yamasaki *et al.* 1997). Because that form is associated with low hydrolysis of sarin, the authors hypothesized that it could make the Japanese population more sensitive to the toxicity of sarin, which might contribute to their morbidity and mortality after the terrorist attacks in Japan. Yamada *et al.* (2001), however, reported that of 10 of the victims of the Tokyo attack, 7 expressed the PON1 Q allele (6 QR, 1 QQ). The genotype that confers high hydrolysing activity toward sarin, therefore, did not appear to play a role in protecting those exposed against the toxicity of sarin.

The relationship between illness in Gulf War veterans and the PON1 genotype and serum acetylcholinesterase (AChE) activity has been investigated by Haley *et al.* (1999). The enzyme activity, or ability to metabolize acetylcholine, can be quantified in serum samples from the veterans. That activity is, in part, a function of the genotype of the veteran. Ill veterans ($n=25$) were more likely than controls ($n=20$) to possess the R allele (genotype RR or QR; OR 3.50; CI 0.26–2.80) and to exhibit lower PON1 type Q arylesterase activity. That study raises the possibility that the R allele represents a risk factor for illness in Gulf War veterans, but in a nested case-control study, Hotopf *et al.* (2003) did not find any differences in PON1 activity between symptomatic and asymptomatic Gulf War veterans. Those researchers studied symptomatic Gulf War veterans, healthy Gulf War veterans, symptomatic Bosnia peace-keeping veterans and symptomatic non-deployed military controls. The main outcome measures were PON1 activity and genotype for PON1-55 and -192. The authors observed statistically significant differences in PON1 activity among the four groups, but the two gulf groups did not differ in PON1 activity. However, those deployed to the gulf had significantly lower PON1 activity than the non-Gulf War groups (median difference 70.9; 95% CI 20.2–121.5; $p=0.012$); the differences were not explained by PON1 polymorphisms. PON1 activity was lower in Gulf War veterans than in military control groups. The effect is independent of ill health in Gulf War veterans.

Those studies do not entirely clarify the role of PON1 in Gulf War veterans. A study by Mackness *et al.* (2000) suggests that symptomatic Gulf War veterans have lower PON1 activity, but this is not explained by the various genotypes in Hotopf *et al.* (2003). Nonetheless, the decreased activity of PON1 would result in an increased susceptibility to OP insecticides and gases, such as sarin.

(c) 2004 sarin update

Following completion of the 2000 review, several new studies on sarin effects in laboratory animals were published. In particular, the VA Gulf War Research Advisory Committee, chaired by Mr James Binns, concluded that the new animal studies required a revision of earlier IOM committee conclusions on the lack of evidence supporting human health effects from

Table 7. Sarin health effects studies used in IOM's report 'Gulf War & Health: updated literature review of sarin,' 2004—non-Gulf War veteran studies previously reviewed in 'Gulf War & Health: volume 1'. (Abbreviations: IES-R-J, impact of event scale; PTSD, post-traumatic stress disorder; SES, socio-economic status.)

reference	type of study and study population	exposure determination	health outcome, and how and when measured	results	adjusted RR or OR (95% CI or <i>p</i>)	limitations
Page (2003)	follow-up study of military volunteers for 1955–1975 Edgewood, Maryland, programme; one group with anticholinesterase exposure (<i>n</i> = 1339) versus exposed to two or more non-anticholinesterase agents (<i>n</i> = 1359) versus no chemical test (non-exposed) (<i>n</i> = 1324)	military deliberately administered 250 agents, including sarin, cyclosarin, and 13 other anticholinesterases; doses not carefully recorded; sarin doses may have ranged from 3.0 to 4.0 µg kg ⁻¹	mortality records from VA and Social Security Administration, survey of neuropsychologic impairment, illness attitudes, peripheral nerve disease, vestibular dysfunction, sleep disorders, and reproductive history; surveys conducted at least 25 years after exposures	no excess mortality from particular conditions, but less mortality from all causes in anticholinesterase-exposed than unexposed; fewer attention problems in anticholinesterase-exposed versus other warfare agents; greater sleep disturbances than non-exposed	RR for all-cause mortality 0.89 in anticholinesterase-exposed versus non-exposed (95% CI 0.68–0.99)	lack of dose information and inability to assemble a sarin-only cohort
Nishiwaki <i>et al.</i> (2001)	56 exposed rescue workers and police officers versus 52 non-exposed matched controls in same departments	high- and low-exposure group from self-reports of hospitalizations versus outpatient treatment	five neurobehavioural tests, stabilometry, vibration perception, and IES-R-J and general health questionnaire conducted 3 years after exposure	dose-effect relationship with backward digit span memory performance, using multiple logistic regression, and findings independent of trauma symptoms; adjusted tapping interval for dominant hand worse in high-exposed group than controls; stabilometry measures with eyes open significantly worse in low-exposed group than controls, but no dose effect	backward digit span: high-dose adjusted OR, 3.19 (95% CI 1.06–10.38) and low-dose OR, 1.17 (95% CI 0.42–3.23)	not clear whether medical-record check conducted to verify self-reported level of exposure
Kawana <i>et al.</i> (2001)	follow-up of 582 patients treated at St Luke's hospital in Toyko at 2, 3 and 5 years, no control group	not clear from study	33-item mailed questionnaire at three times (1997, 1998, 2000; 2, 3 and 5 years after exposure) covering physical and psychologic symptoms related to sarin; PTSD assessed three ways	most-frequent symptoms: eye symptoms (tiredness of eyes, dim vision, difficulty focusing), tiredness, fatigue, stiff muscles, headache, depressed mood; prevalence (1997, 1998, 2000): DSM-IV PTSD (2.8, 2.9, 2.1%); partial PTSD (7.1, 7.3, 8.4%); PTSD–Nakano (12.4, 9.7, 14.1%)	no control group, low response rate, methods of dose determination or subject selection not reported	

Table 8. Sarin health effects studies used in IOM's report 'Gulf War & Health: updated literature review of sarin,' 2004—studies of Gulf War veterans. (Abbreviations: CBW, chemical or biologic warfare; CFS, chronic fatigue syndrome; CI, confidence interval; DoD, Department of Defense; GI, gastrointestinal; MCS, multiple chemical sensitivity; NBC, nuclear, biologic and chemical warfare; OR, odds ratio; POMS, profile of mood states; PTSD, post-traumatic stress disorder; RR, relative risk; UK, United Kingdom).

reference	population	exposure assessment for relevant agents	timeframe and health-outcome assessment	results	limitations
<i>Studies of veterans potentially exposed at Khamisiyah not reviewed in GW1</i>					
Smith <i>et al.</i> (2003)	431 762 active-duty US military deployed to Gulf War divided into two groups: non-exposed ($n=318\ 458$), possibly exposed ($n=99\ 614$); active-duty includes all active duty up to 10 years after the war (until separation) and reserve only while on active-duty status (follow-up to Gray <i>et al.</i> 1999)	second exposure model by DoD of nerve agent release data, meteorological models, and atmospheric removal mechanisms combined with troop positions	DoD hospitalizations (1991–2000) for any cause, diagnoses from 15 categories and specific diagnoses proposed by expert panel	using Cox modelling, 2 of 37 models showed an increase adjusted risk of hospitalization for cardiac dysrhythmias, circulatory system diseases (RR 1.07; 95% CI 1.0–1.13), specifically for cardiac dysrhythmias (RR 1.23; 95% CI 1.04–1.44)	limited to DoD hospitals; hospitalization data available for only active and reserve Gulf War veterans who remained on active duty or retired with medical benefits after the end of the war; no outpatient data available
Gray <i>et al.</i> (1999)	349 291 active-duty US military deployed to Gulf War divided into three groups: not exposed ($n=224\ 804$); uncertain low-dose exposure ($n=75\ 717$); estimated subclinical exposure ($n=48\ 770$)	first exposure model by DoD of nerve agent release data, meteorological models combined with troop positions	DoD hospitalizations (1991–1995) for any cause, diagnoses from 15 categories and specific diagnoses proposed by expert panel	using Cox modelling, none of the models suggested a dose-response relation or neurologic sequelae	limited to DoD hospitals; hospitalization data available for only active and reserve Gulf War veterans who remained on active duty or retired with medical benefits after the end of the war; no outpatient data available
McCauley <i>et al.</i> (2002)	923 Khamisiyah-exposed US Gulf War veterans versus 927 Khamisiyah non-exposed Gulf War veterans versus 1369 non-Gulf War-deployed veterans from Oregon, Washington, California, Georgia, or North Carolina	exposure defined by DoD as troop location within a 50 km radius of Khamisiyah	computer-assisted telephone interview about Khamisiyah-related exposures, medical conditions diagnosed by a physician, hospitalizations, and disability; interview conducted 8 years after Khamisiyah demolition	no differences between Khamisiyah-exposed and Khamisiyah-non-exposed Gulf War veterans in health conditions; deployed troops significantly more likely than non-deployed troops to report physician-diagnosed high blood pressure (OR 1.7; 95% CI 1.3–2.4), heart disease (OR 2.5; 95% CI 1.1–6.6), slipped disk or pinched nerve (OR 1.5; 95% CI 1.1–2.0), PTSD (OR 14.9; 95% CI 5.6–60.9), hospitalization for depression (OR 5.1; 95% CI 1.5–32.1), periodontal disease (OR 1.8; 95% CI 1.2–2.8)	self-reported conditions recalled 9 years after exposure, DoD's models of nerve agent exposure not yet available, not representative of entire Gulf War cohort

(Continued.)

Table 8. (Continued.)

reference	population	exposure assessment for relevant agents	timeframe and health-outcome assessment	results	limitations
McCauley <i>et al.</i> (2001)	2918 veterans from Oregon, Washington, California, Georgia, or North Carolina	exposure defined by DoD as troop location within a 50 km radius of Khamisiyah	computer-assisted telephone interview about Khamisiyah-related exposures, 24-item symptom checklist during Khamisiyah operations, and current symptom checklist	no significant differences between Khamisiyah-exposed versus non-exposed in current or past symptoms; numerous significant differences between Khamisiyah-witnesses versus non-witnesses in past and current symptom reporting; current symptoms in Khamisiyah-witnesses versus non-witness: tingling or burning sensations of the skin (OR 1.7; 95% CI 1.1–2.8), changes in memory (OR 1.7; 95% CI 1.2–2.4), difficulty sleeping (OR 2.0; 95% CI 1.2–3.5), persistent fatigue (OR 1.8; 95% CI 1.2–2.6), depression (OR 1.6; 95% CI 1.1–2.4), and bloody diarrhoea (OR 3.1; 95% CI 1.6–6.0)	self-reported symptoms recalled 9 years after exposure, DoD's models of nerve agent exposure not yet available, not representative of entire Gulf War cohort
<i>Self-reported exposures: population-based studies</i>					
Reid <i>et al.</i> (2001)	subgroups of UK veterans meeting case criteria for MCS and CFS (same cohort as Unwin <i>et al.</i> 1999)	three relevant environmental exposures: 'NBC suits', 'hear chemical alarms', 'chemical/nerve gas attack'	symptom questionnaires, exposure questionnaire, both 6–7 years after Khamisiyah demolition	in Gulf War veterans, MCS associated with 'hear chemical alarms' (OR 2.5; 95% CI 1.0–5.9), 'chemical/nerve gas attack' (OR 4.6; 95% CI 1.6–13.3), CFS associated with 'hear chemical alarms' (OR 2.5; 95% CI 1.2–5.3)	self-reported symptoms and exposures
Suadicani <i>et al.</i> (1999)	686 Gulf War-deployed peacekeepers versus matched controls from Danish armed forces	one relevant exposure: 'nerve gas'	symptom questionnaires, exposure questionnaire up to 6 years after return	in Gulf War cohort, 'nerve gas' not significantly associated with neuropsychological symptoms	self-reported symptoms and exposures
Ishoy <i>et al.</i> (1999a)	686 Gulf War-deployed peacekeepers versus matched controls from Danish armed forces (same cohort as Suadicani <i>et al.</i> 1999)	one relevant exposure: 'nerve gas'	symptom questionnaires (GI symptoms), exposure questionnaire, clinical examination up to 6 years after return	after multivariate adjustment, nerve gas not significantly associated with GI symptoms	self-reported symptoms and exposures

(Continued.)

Table 8. (Continued.)

reference	population	exposure assessment for relevant agents	timeframe and health-outcome assessment	results	limitations
Spencer <i>et al.</i> (2001)	random sample ($n = 2343$) of 23 711 Gulf War veterans from Oregon or Washington state, nested case-control study	three relevant exposures: 'chemical decontamination bottles', 'inadequate protection during chemical/SCUD alarms', 'worked around chemical warfare agents'	exposure questionnaire, symptom questionnaires collected 4–7 years after Khamsiyah demolition, clinical examination to verify case of unexplained illness	by simple logistic regression, cases of unexplained illness ($n = 241$) more likely than healthy Gulf War-deployed controls ($n = 113$) to report 'inadequate protection during chemical/SCUD alarm'	self-reported symptoms and exposures, multivariate analysis not performed on exposures of interest
Kang <i>et al.</i> (2002)	11 441 US veterans deployed to Gulf War versus 9476 non-Gulf War-deployed, nested case-control study	one relevant exposure: 'nerve gas'	potentially new neurologic syndrome via factor analysis, symptom questionnaires, exposure questionnaire, surveys conducted in 1995	'nerve gas' among nine self-reported exposures at least three times more common in 277 Gulf War-deployed veterans (cases) with these symptoms (loss of balance or dizziness, speech difficulty, sudden loss of strength, tremors or shaking) than in Gulf War-deployed non-cases (42.3% of cases reported nerve gas exposure versus 4.6% of Gulf War-deployed non-cases)	self-reported symptoms and exposures, no analysis for dose-response relationship
Kang <i>et al.</i> (2003)	11 441 US veterans deployed to Gulf War versus 9476 non-Gulf War-deployed, nested case-control study	'had worn chemical protective gear or heard chemical alarms sounding' was one of three combat stressors; other combat stressors: 'had been involved in direct combat duty' and 'had witnessed any deaths'	PTSD, CFS; surveys conducted from 1995 to 1997	PTSD excess (adjusted OR 3.1; 95% CI 2.7–3.4), CFS excess (adjusted OR 4.8; 95% CI 3.9–5.9), PTSD prevalence increased with combat stress intensity, from 3.3 to 22.6% (test for trend, $p > 0.15$)	self-reported symptoms and exposures, lack of analysis solely of sarin-related exposure
<i>Studies reviewed in GW1</i>					
Iowa Persian Gulf Study Group (1997)	1896 deployed veterans from Iowa as home of record versus 1799 non-deployed veterans from Iowa as home of record	one relevant exposure: 'chemical warfare agents'	symptom questionnaires, exposure questionnaire no more than 6 years after Khamsiyah demolition	in Gulf War veterans, exposure to 'chemical warfare agents' associated with symptoms of cognitive dysfunction (prevalence difference, 6.8%; $p < 0.001$), depression (prevalence difference, 8.6%; $p < 0.001$), fibromyalgia (prevalence difference, 8.1%; $p < 0.0$)	self-reported symptoms and exposures, low proportion of minority-group subjects, internal validation of responses not assessed, no adjustment for multiple comparisons, multiple associations between variety of exposures and variety of outcomes

(Continued.)

Table 8. (Continued.)

reference	population	exposure assessment for relevant agents	timeframe and health-outcome assessment	results	limitations
Goss Gilroy Inc. (1998a,b)	3113 Canadian veterans deployed to Gulf War versus 3439 deployed elsewhere	over 30 exposures divided into six categories; one category was relevant: 'chemical warfare agents' (nerve gas and mustard gas or other blistering agent)	symptom questionnaires, exposure questionnaire 6 years after Khamisiyah demolition	in Gulf War cohort, exposure to 'chemical warfare agents', in multivariate analysis, not associated with symptoms of cognitive dysfunction, chronic fatigue, fibromyalgia; significantly associated with PTSD diagnosed by health-care provider (OR 5.25; 95% CI 1.36–20.30), major depression (OR 3.66; 95% CI 1.21–11.03), anxiety (OR 5.59; 95% CI 1.48–21.07)	self-reported symptoms and exposures, subset of Canadian veterans not exposed to many agents (because they were based at sea) reported symptoms as frequently as did land-based veterans, no adjustment for multiple comparisons, multiple associations between various exposures and various outcomes, not clear which relevant exposures related to outcome
Unwin <i>et al.</i> (1999)	2735 UK veterans deployed to Gulf War versus 2393 deployed to Bosnia versus 2422 deployed elsewhere	three relevant environmental exposures: 'NBC suits', 'hearing chemical alarms', 'chemical/nerve gas attack'	symptom questionnaires, exposure questionnaire, both 6–7 years after Khamisiyah demolition	in Gulf War cohort only, three exposures associated with chronic multi-symptom illness and PTSD; for chronic multi-symptom illness, ORs for three exposures, 2.2–2.7, CIs do not include 1; for PTSD, ORs for the three exposures, 2.1–3.1, CIs do not include 1	self-reported symptoms and exposures, lack of adjustment for interrelationships between multiple exposures, use of <i>p</i> value of 0.05 despite multiple comparisons
<i>Self-reported exposures: military-unit-based studies</i>					
White <i>et al.</i> (2001)	273 deployed veterans from Massachusetts (Fort Devens) and New Orleans versus 50 Germany-deployed veterans, 1994–1996 (same cohort as Proctor <i>et al.</i> 1998)	one relevant exposure: 'chemical or biological warfare (CBW) agents'	15 neurobehavioural tests: WAIS-R, tests of attention, executive function, motor-psychomotor, visuospatial, memory, mood (POMS), motivation; exposure questionnaires; diagnostic interviews for PTSD; 3–5 years after Khamisiyah demolition	in regression analyses, Gulf War veterans exposed to CBW agents (versus non-exposed) more likely to have mood, memory, cognitive deficits; in particular, their scores significantly worse ($p < 0.05$) on POMS tension and confusion scales, three tests of recall memory, backward digit span test (WMS-R) of attention, executive system function (after controlling for PTSD and depression)	self-reported exposures, not representative of entire Gulf War cohort
Wolfe <i>et al.</i> (2002)	1290 Gulf War-deployed veterans from Massachusetts (Ft. Devens), 1997 (same cohort as Proctor <i>et al.</i> 1998)	two relevant exposures: 'exposure to poison gas or germ warfare' and 'placement on formal alert for chemical and biological warfare'	psychologic-symptom questionnaire, combat-exposure questionnaire, 6 years after Khamisiyah demolition	in multivariate analysis, none of two exposures significantly associated with mild to moderate or severe multi-symptom illness	self-reported exposures, limited representativeness of entire Gulf War cohort

(Continued.)

Table 8. (Continued.)

reference	population	exposure assessment for relevant agents	timeframe and health-outcome assessment	results	limitations
Nisenbaum <i>et al.</i> (2000)	1002 US veterans from four Air Force units; nested case-control survey of 459 Gulf War veteran cases of chronic multi-symptom illness versus 543 controls without chronic multi-symptom illness (follow-up to Fukuda <i>et al.</i> 1998)	one relevant exposure: 'thought biological or chemical weapons were being used'	symptom questionnaires, exposure questionnaire, 4 years after Khamisiyah demolition	'thought biological or chemical weapons were being used', in logistic regression adjusting for presence of other exposures, associated with criteria for severe case of multi-symptom illness (OR 3.46; 95% CI 1.73–6.91) and mild-moderate case (OR 2.25; 95% CI 1.54–3.27)	self-reported symptoms and exposures, no reporting on exact time of exposure, exclusion of Gulf War veterans no longer in active service, no adjustment of <i>p</i> value despite multiple comparisons, limited representativeness of entire Gulf War cohort
Gray <i>et al.</i> (1999)	527 active-duty US Seabees formerly deployed to Gulf War versus 969 non-deployed veterans from same Seabee commands	one relevant exposure: 'chemical warfare'	symptom questionnaire, exposure questionnaire, clinical examination, handgrip strength, pulmonary function, serum collection, covered from 1991 to 1995	'chemical warfare' not 1 of the 11 exposures studied in analyses	self-reported symptoms and exposures, potential recall bias in symptom reporting, moderate to low response rate, exclusion of veterans no longer in active service, results of multivariate analysis not reported, limited representativeness of entire Gulf War cohort
Gray <i>et al.</i> (2002)	Gulf War-era active-duty and reserve US Seabees: 3831 Gulf War Seabees, 4933 Seabees deployed elsewhere, 3104 non-deployed Seabees (follow-up to Gray <i>et al.</i> 1999)	one relevant exposure: 'use of gas masks'	health behaviours; physician-diagnosed illnesses; self-reported persistent or recurring medical problems; exposure questionnaire, at least 6 years after Khamisiyah demolition	22% of Gulf War veterans met definition of Gulf War illness: 1 or more physician-diagnosed multi-symptom illnesses or at least 12 self-reported persistent or recurring medical problems; in multivariate analysis, Gulf War illness associated with 'use of gas masks' (OR 1.40; 95% CI 1.07–1.84)	conducted 5–7 years after Gulf War, self-reported symptoms and exposures, potential recall bias in symptom reporting, limited representativeness of entire Gulf War cohort
Kroenke <i>et al.</i> (1998)	18 495 US Gulf War veterans in DoD comprehensive clinical evaluation programme	one relevant exposure: 'nerve gas/agents'	physician-administered symptom checklist, exposure questionnaire, combat and work-loss questionnaires no more than 6 years after Khamisiyah demolition	no association between individual symptoms and specific exposures	included only subjects who presented for evaluation, self-reported symptoms and exposures, lack of control group, lack of statistical analysis, limited representativeness

(Continued.)

Table 8. (Continued.)

reference	population	exposure assessment for relevant agents	timeframe and health-outcome assessment	results	limitations
<i>Studies reviewed in GW1</i>					
Proctor <i>et al.</i> (1998)	291 deployed veterans from Massachusetts (Ft Devens) and New Orleans versus 50 Germany-deployed veterans, 1994–1996	one relevant exposure: 'chemical or biological warfare (CBW) agents'	symptom questionnaires; exposure questionnaires; clinical evaluations for PTSD; evaluations conducted in 1991, 1993–1994 and 1995–1997	in Gulf War cohort, exposure to CBW agents, in multivariate analysis, significantly associated with musculoskeletal ($p=0.001$), ^a neurologic symptoms ($p=0.013$), ^b neuropsychologic ($p=0.009$), ^c psychologic ($p=0.001$) symptoms	self-reported symptoms and exposures, moderate to low response rate, limited representativeness of entire Gulf War cohort
Haley & Kurt (1997)	23 US veterans with up to three newly defined syndromes (derived from factor analysis) versus 229 veterans without newly defined syndromes	one relevant exposure: 'chemical warfare agents'	symptom questionnaire, exposure questionnaire, within 5 years of Gulf War	'chemical warfare agents' exposure associated with one of three newly defined syndromes ('confusion-ataxia') (RR 7.8; 95% CI 2.3–25.9); synergy between exposure to 'chemical warfare agents' and scores on scale of advance adverse effects from pyridostigmine bromide in predicting 'confusion-ataxia syndrome'	self-reported symptoms and exposures, no control group in original cohort, limited representativeness of entire Gulf War cohort

^a Joint pains, backaches and neckaches or stiffness.^b Headaches, numbness in arms or legs and dizziness.^c Difficulties in learning new material, difficulty in concentrating and confusion.^d Inability to fall asleep, frequent periods of feeling depressed, and frequent periods of anxiety or nervousness.

trace level exposure to chemical warfare agents including sarin. The two laws that established this formal review process also anticipated the need for periodic updates as new scientific studies became available. Therefore, in February 2003, VA requested the IOM to update their 2000 investigation on the possibility of sarin causing long-term health effects, which they completed in August 2004.

For their update, the IOM committee focused on about 250 peer-reviewed articles published *after* their earlier 2000 report, including 19 epidemiological studies of sarin health effects (tables 7 and 8), as well as a wide range of animal studies. These included three studies of non-Gulf War veterans, four studies of Gulf War veterans potentially exposed at Khamisiyah, six population-based studies of US and UK Gulf War veterans using self-reported exposures and six studies of specific military units of Gulf War veterans also based on self-reported exposures. All of the studies reviewed in the initial IOM investigation were also considered in the update.

As with their earlier review, non-Gulf War veteran studies were based upon: (i) US military volunteers who had been experimentally exposed decades ago to non-lethal doses of sarin and other chemical warfare agents; (ii) industrial workers with documented acute exposure to sarin; and (iii) victims of the sarin terrorist attacks in Matsumoto City in 1994 and Tokyo in 1995. The committee also considered other relevant issues, including exposure to multiple chemicals at the same time and genetic susceptibilities. As with previous IOM committees, the new committee included toxicologists as well as epidemiologists and other public health scientists, to ensure that both animal and human data were considered.

The committee noted that virtually all human sarin studies lack good exposure data. For example, following their 2000 report, DoD exposure modelling for the Khamisiyah sarin incident was criticized as inaccurate by the US Congressional GAO. The IOM committee also noted the significant uncertainties surrounding DoD Khamisiyah exposure assessments as, 'none of the studies using exposure information showed persistent neurological effects in Khamisiyah-exposed troops compared to non-Khamisiyah exposed troops. Because of the uncertainty in the [Khamisiyah] exposure assessment models... those studies do not provide strong evidence for or against the presence of neurologic effects.' That is, studies based upon the DoD Khamisiyah sarin exposure modelling added little to our understanding of long-term sarin health effects. Rose & Brix (2006) consider the data on long-term damage to the peripheral nervous system in Gulf war veterans, also concluding that the evidence for any such effects is not compelling, suggesting that even if there was sarin exposure, it has not resulted in damage to the peripheral nervous system.

The 2004 IOM update confirmed the findings of the earlier IOM analysis, that: (i) there is sufficient evidence of a causal relationship between exposure to sarin and a dose-dependent acute cholinergic syndrome that is evident seconds to hours subsequent to sarin exposure and resolves in days to months; (ii) there is limited/suggestive evidence of an association between

exposure to sarin at doses sufficient to cause acute cholinergic signs and symptoms and a variety of subsequent long-term neurological effects; and (iii) there is inadequate/insufficient evidence to determine whether an association does or does not exist between exposure to sarin and subsequent long-term cardiovascular effects (this last finding was not contained in the 2000 report).

The committee also reported that the new published data from experimental animals that had precipitated the interest in updating the earlier IOM review, which were designed to mimic the potential exposures in the Gulf War, were an important step in 'determining whether a biologically plausible mechanism could underlie any long-term effects of low exposure to chemical nerve agents, but more work needs to be conducted to elucidate potential mechanisms and clarify how the cellular effects are related to any clinical effects that might be seen.'

In conclusion, exposure to sarin nerve agent remains an implausible cause of the illnesses experienced by Coalition Armed Forces. No military or intelligence authority accepts the proposition advanced in some quarters that there was deliberate use of nerve agents by Iraqi forces at the start of the ground war, which remained undetected and caused no immediate acute poisoning signs and symptoms at the time (in contrast to the Japan sarin terrorist attacks). Turning to the accidental destruction of sarin containing munitions at Khamisayah at the end of hostilities, the absence of any acute effects on personnel at the site also speaks against a serious contamination. Likewise, United Kingdom, Canadian, Australian and Danish military personnel, all of whom have experienced changes in subjective ill health similar to those of US personnel, were all too far distant, or even not in theatre, to have experienced exposure likely to cause any health effects.

On the other hand, the belief in exposure to sarin is the single strongest risk factor seen in studies of Gulf veterans. The prevalence of those who believe the cause of their ill health varies—being greater in the US than in the UK—but the strength of the association is very similar (Stuart *et al.* 2003).

(d) *Pyridostigmine bromide*

The drug pyridostigmine (PB), as either its bromide or iodide salt, is a reversible cholinesterase inhibitor used as a chemical warfare agent prophylaxis by some Coalition troops during the 1991 Gulf War. The IOM committee reviewed the large number of clinical and the fewer epidemiological studies conducted for this drug, as well as an extensive toxicological literature based upon laboratory animals. They noted that PB has been widely used for more than 40 years in the conventional treatment of myasthenia gravis in much larger doses.

Based upon their review of this abundant literature, the committee reached two conclusions: (i) that there is 'sufficient evidence of an association' between this medication and *transient acute* cholinergic effects in doses normally used in treatment and for diagnostic purposes; and (ii) that there is 'inadequate/insufficient evidence' to determine whether an association does or does not exist between PB and any long-term adverse health effects.

The committee reached several conclusions about the acute effects of PB: 'a large number of clinical studies report acute, transient cholinergic effects in normal volunteers and patients with a wide variety of clinical disorders given PB as a diagnostic test of hypothalamic pituitary function and patients with myasthenia gravis treated with the drug for extended periods...' PB is routinely used to treat patients diagnosed with myasthenia gravis with daily doses from 120 to 600 mg given for the lifetime of the patient. The committee reported that studies show about 34% of patients receiving PB have one or more, mostly mild, side effects, usually gastrointestinal, although a few experience other cholinergic symptoms such as hypersalivation, increased perspiration, urinary urgency, increased bronchial secretion and blurred vision. Patients rarely stop taking the drug because of abdominal complaints. By comparison, during the 1991 Gulf War, acute accidental poisoning with PB in doses ranging from 390 to 900 mg resulted in mild to moderate cholinergic symptoms within several minutes of ingestion, which lasted up to 24 h.

The committee explained their key finding of 'inadequate/insufficient evidence to determine whether an association does or does not exist between PB and long-term adverse health effects.' 'The epidemiologic data do not provide evidence of a link between PB and chronic illness in Gulf War veterans. Most epidemiologic studies of Gulf War veterans focused on whether a unique Gulf War syndrome exists and on defining its characteristics. Only two epidemiologic studies specifically investigated the possible association of PB use and chronic symptoms among Gulf War veterans (Haley & Kurt 1997; Unwin *et al.* 1999).'

The IOM committee noted: 'the suggestion of a unique manifestation of organophosphate-induced delayed polyneuropathy associated with PB exposure alone or in combination with other wartime exposures, in the absence of acute symptoms of organophosphate toxicity, requires further investigation.' 'Although Haley and colleagues provide evidence that chronic neurological changes are present in a small number of ill Gulf War veterans compared to a small number of well veterans from the same unit, the validity and causal nature of this association are uncertain due to the large potential for selection and information biases in this study population and the lack of a non-deployed comparison group.' This echoes concerns expressed in other peer-reviewed literature and expert reports on either side of the Atlantic, such as the UK Medical Research Council review.

In addition, the evidence that some types of chronic neuropsychological changes may be linked to acute responses to administration of PB, also suggested by Haley & Kurt (1997), is limited by the lack of consistency with results from toxicological and clinical studies; uncertainty about the selection, administration, and interpretation of the neuropsychological tests employed; the highly select nature of the small number of Gulf War veterans studied; and the lack of comparable studies in a non-deployed comparison group.

Noting that in general studies have reported a general association between ill health and recall of hazardous exposures, rather than specific links, the IOM

committee concluded: 'the other epidemiologic study was of UK servicemen (Unwin *et al.* 1999), and all exposures studied (PB, diesel or petrochemical fumes, oil fire smoke, viewing dismembered bodies, etc.) showed an association of similar magnitude with adverse symptoms. Recall and reporting bias may also explain this finding. Thus, neither of these two studies provides a basis for determining that a specific association between PB and chronic adverse health effects exists.'

Similarly, the 2003 MRC report noted that most UK armed service personnel deployed to the Gulf were given PB nerve agent pre-treatment tablets. They also noted that the acute effects of PB are well characterized in human and animal studies, and are typical of other agents that inhibit AChE. Further, PB is routinely used to treat myasthenia gravis, a disease of nerve/muscle junctions, at doses generally much higher compared to that used to protect against nerve agents, and over much longer periods. They also noted that the effects of PB in combination with other agents such as insecticides and insect repellents, vaccines, genetics or stress are not known and are difficult to study.

(e) *Natural experiments*

Canada's experience as a Gulf War Coalition member provided a unique 'natural experiment' in deployment-related veterans' health effects. Three Canadian ships left for the Gulf War in August of 1990, and all three remained in the Gulf for the duration. One of the three ships (the HMCS Protecteur) rotated its entire crew between Christmas and New Year of 1990. Because they served early in the deployment prior to any hostilities, the first crew did not have exposure to most of the common Gulf War hazards of concern, including PB, anthrax or plague vaccine, oil-well smoke, chemical or biological warfare agents (including from the Khamsiyah incident), pesticides including OP pesticides, etc. The HMCS Protecteur did have DU weapons, and apparently although practice firing of DU rounds occurred, no rounds were fired in a conflict situation.

A study of the health of the sailors involved on this ship found that the initial crew who served only in 1990 and prior to the outbreak of actual hostilities later reported increased rates of a wide range of symptoms compared to controls, and at a rate similar to Canadian sailors who had served on ship actually during the conflict (Goss Gilroy 1998a,b). In other words, these early sailors manifested a 'Gulf War deployment' effect, even though their prime exposure was through seeing the conflict second hand while back in Canada.

Similarly, other Coalition troops who served in the Gulf War but had little or no exposure to combat or other Gulf War-related environmental hazards are reported to have war-related health problems, compared to matched controls. Danish Gulf War veterans were nearly all involved only in peacekeeping or humanitarian roles during the 1991 Gulf War (Ishoy *et al.* 1999a,b). Danish Gulf War Veterans have been reported to have significantly higher prevalence of self-reported neuropsychological symptoms up to six years after their return associated with various exposures (Suadcani *et al.* 1999). Reported symptoms include concentration, memory problems, repeated fits of headache, balance disturbances or fits of dizziness, abnormal fatigue not

caused by physical activity, and problems sleeping all night. A wide range of 'exposures' were strongly associated with neuropsychological symptoms. Each of 17 self-reported symptoms was significantly more prevalent among deployed veterans compared to controls, and many of the symptoms were correlated with each other. Moreover, Danish veterans reported higher prevalence of unspecific symptoms such as repeated fits of headache, fatigue, memory and concentration difficulties, sleep disturbances, agitation, dyspnoea, diseases of the skin, and intermittent fever. Researchers noted that this symptom pattern was consistent with the findings among US Gulf War veterans, even though Danish Gulf War veterans were predominantly deployed after the war in peace-keeping missions (Ishoy *et al.* 1999a,b).

An obvious concern about PB health effects is that the drug is prescribed as a means of treating a neuromuscular disease (myasthenia gravis)—yet a common symptom among Gulf War veterans is muscular weakness or fatigue—is there a connection? The IOM committee reviewed clinical studies of PB, fatigue and neuromuscular effects, and noted one report of a group of 17 patients with post poliomyelitis syndrome, who along with 10 controls were studied for response to PB and similar drugs. Given 180 mg PB daily for one month, nine of the 17 patients reported improvement in fatigue, and continued using the drug for an average of 1.2 years, despite mild gastrointestinal effects (Trojan *et al.* 1993). Thus, 'it appears that PB seems to be well tolerated and without significant neuromuscular side effects at the prescribed dose.'

(f) Interactions between Gulf War hazardous exposures

The 2000 IOM committee also examined the possibility that various Gulf War exposures in combination might interact to cause illness. They noted there are limited studies on pharmacological interactions between PB and other Gulf War risk factors, including the OP pesticide chlorpyrifos, and the insect repellent *N*-diethyl-*m*-toluamide (DEET). Co-exposure to these three agents at sub-lethal doses to hens over 2 months resulted in increased toxicity (Abou-Donia *et al.* 1996a). Although the IOM committee noted that the pathology and neurological impairment reported in this study were 'hallmarks' of OPIDN, nevertheless 'symptoms of this neurotoxic disorder are not consistent with those reported in Gulf War veterans' illnesses. Similarly, none of the agents involved inhibits neurotoxic esterases (a target marker for OPIDN potency) at levels consistent with being capable of causing this disease in humans. Similarly, co-exposure to hens of combinations of PB and DEET along with permethrin also showed increased toxicity, possibly because two of these agents are esterase inhibitors and the third is an ester (Abou-Donia *et al.* 1996b). Finally, co-exposure to large amounts of these three agents to rats increases their lethality (McCain *et al.* 1997), although the relevance of such a dosing regime to humans is not clear. Moreover, the IOM committee concluded, 'there is no *a priori* reason to suspect that PB is capable of causing OPIDN,' and 'there are insufficient data to determine whether exposure to other chemicals, either before or after PB,

enhances its potential to produce delayed neurotoxicity.' Relative to human health effects, the committee similarly concluded that the lack of data supporting an association between PB exposure and long-term adverse health effects was true 'particularly when PB exposure occurs in combination with other combat exposures.'

(g) Vaccines

All military service personnel are routinely vaccinated against a wide variety of common infectious diseases, and against certain military-specific diseases, as indicated. Some veterans have expressed concerns that these vaccinations, or some combination of vaccines, could result in long-term health consequences. The IOM committee noted the difficulty of studying this issue among actual Gulf War veterans, again because of poor data on who actually received the vaccines. DoD recorded that about 311 000 doses of the anthrax vaccine were sent to the Gulf War theatre, and about 150 000 US service members received at least one vaccination. However, little information is available on who actually received them. Similarly, according to DoD, about 138 000 doses of botulinum toxoid were sent to the Gulf, and about 8000 US service members were estimated to have received the vaccine, but medical records provide little information about who actually were the recipients.

The peer-reviewed scientific literature available to the committee on adverse effects among humans from anthrax and botulinum toxoid vaccines included results from human volunteer studies, US post-market surveillance via the voluntary Vaccine Adverse Event Reporting System, and active surveillance from clinical studies. The committee noted that studies on these two vaccines primarily involved passive surveillance with only short follow-up periods relative to the periods that concern Gulf War veterans. Similarly, available studies were often limited by small sample size, involvement of multiple different vaccinations, large numbers of potential health outcomes evaluated, and lack of unique symptoms specific to vaccination.

The committee found only one randomized peer-reviewed study of the type of anthrax vaccine used in the United States (Brachman *et al.* 1962), and it involved no long-term monitoring for adverse outcomes. The committee also had data from animal studies, including anthrax vaccination of agricultural live-stock.

Not surprisingly, the committee concluded, 'there is a paucity of published peer-reviewed literature on the safety of the anthrax vaccine.' Nevertheless, they also concluded that published studies have not reported any significant adverse effects. Similarly, the committee found few published peer-reviewed studies on potential adverse health effects from the botulinum toxoid vaccine administered to humans. The small number of limited studies probably contributed to their default conclusion of 'inadequate/insufficient evidence of an association' for long-term health effects.

Anthrax vaccine

The IOM committee found: (i) that there is sufficient evidence of an association between the anthrax vaccination and transient acute local and systemic effects (e.g. redness, swelling, fever), as is typically associated with

vaccination; and (ii) that there is inadequate/insufficient evidence to determine whether an association does or does not exist between the anthrax vaccination and *long-term* adverse health effects.

Botulinum toxoid

The committee found: (i) that there is sufficient evidence of an association between the botulinum toxoid vaccination and transient acute local and systemic effects (e.g. redness, swelling, fever), as is typically associated with vaccination; and (ii) that there is inadequate/insufficient evidence to determine whether an association does or does not exist between the botulinum toxoid vaccination and long-term adverse health effects.

The 2003 MRC report noted that most UK armed service personnel deployed to the Gulf were vaccinated against various endemic and biological warfare agents including plague, and anthrax. Unlike US troops, vaccination of UK service members included whooping cough (*pertussis*) vaccine which was used to boost the immune response. In general, other vaccines were given in combined doses according to conventional medical procedures. They noted that some UK epidemiologists reported 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.

The 2003 MRC report concluded that 'There is little evidence that vaccination was a cause of Gulf War veterans' illnesses.' 'One study tentatively linked self-reported symptoms to vaccinations and another found that ill Gulf War veterans had differences in some immune system measurements. However, the significance of these findings is unclear.' Moreover, 'No commonly accepted mechanism could account for immune system-related symptoms persisting more than 10 years after vaccination.'

(h) Simultaneous vaccinations

The committee also noted the paucity of peer-reviewed studies on potential effects from multiple simultaneous vaccinations. They focused on studies of three relevant populations, including a group of Finnish military recruits who received numerous vaccinations during their first weeks of service; a group of laboratory workers at DoD's Fort Detrick, Maryland, who received an intensive vaccination regime as part of their occupational safety; and several limited studies of US and UK veterans of the 1991 Gulf War. The committee reported that these studies provided little evidence of long-term adverse effects (beyond the transient localized and systemic effects seen with any vaccination). However, they made it clear that the available evidence was of insufficient quality, consistency or statistical power to allow developing any firm conclusions about the presence or absence of any association between multiple vaccinations and any adverse health outcomes.

Multiple vaccinations

Not surprisingly, the committee concluded that there is 'inadequate/sufficient evidence' to determine whether

an association does or does not exist between multiple vaccinations and long-term adverse health effects.

The IOM committee noted that: 'Certain multiple vaccination regimens can lead to suboptimal antibody responses, but there is little evidence, largely because of a lack of active monitoring, of other adverse clinical or laboratory consequences beyond the transient local and systemic effects seen frequently with any vaccination.' 'No long-term identifiable clinical sequelae attributable to intense long-term immunization occurred in the Fort Detrick cohort. There was some evidence of a chronic inflammatory response, but these changes cannot necessarily be attributed to the vaccinations, since the workers studied were occupationally exposed to a number of virulent microbes. This series of longitudinal clinical studies also had several shortcomings. However, the studies are valuable because careful monitoring did not disclose any evidence of serious unexplained illness in a cohort that received a series of intense vaccination protocols over many years.' 'The UK Gulf War studies provide some limited evidence of an association between multiple vaccinations and long-term multi-symptom outcomes, particularly for vaccinations given during deployment (Unwin *et al.* 1999; Hotopf *et al.* 2000). There are some limitations and confounding factors in these studies, and further research is needed.' Again, these issues are considered in more detail elsewhere in Peakman *et al.* (2006).

(i) Pesticides and solvents

The next 'Gulf War & Health' IOM committee reviewed health effects from pesticides and solvents used in the 1991 Gulf War. In their 2003 report, all of the 21 health effects identified as positively associated with these risk factors were previously well-documented associations between common occupational and environmental hazards and various cancers, neurological, and other specific diseases (table 4). These were primarily various cancers and serious haematological disorders (e.g. leukaemias, non-Hodgkin's lymphoma, multiple myeloma and aplastic anaemia), subtle general neurological effects detected via neurobehavioural tests, and other health effects (i.e. reactive airway dysfunction syndrome, and allergic contact dermatitis).

Nearly all the data the IOM reviewed came from occupational studies involving large or prolonged exposures to industrial workers. Consequently, most positive findings were based upon occupational exposures the committee characterized as 'chronic,' 'high-level,' or at doses 'sufficient to cause poisoning' (the one exception was an association between propylene glycol and insecticides exposure and allergic contact dermatitis).

Occupational studies are clearly relevant, but results from studies of civilian workers may be difficult to extrapolate to military personnel, since civilian workplace exposures are typically much larger and longer compared to the typical Gulf War veteran, or indeed veterans from any era. The committee commented on the absence of exposure data for the 1991 Gulf War, and it is not clear that Gulf War veterans were on average exposed to significantly larger amounts of the common pesticides and solvents used in that conflict compared to any other service members, or US civilians. None of the

committee's findings came from studies of Gulf War veterans themselves.

Some of the positive associations noted in the 2003 IOM report represent a clear public and occupational health issue for humans exposed to high levels of cholinergic poisons such as the OP pesticides and military nerve agents. However, they are probably less relevant to concerns about long-term neurological health effects among veterans of the 1991 Gulf War (table 4). For example, the committee found 'limited/suggestive evidence' of an association between acute OP pesticide poisoning or solvent exposure, and long-term neurobehavioural effects including abnormal results on neurobehavioural test batteries and symptom finds. In fact, a very large body of scientific literature exists showing such long-term effects in the aftermath of acute, generally severe, cholinergic poisoning (see for example Brown & Brix 1998). As a result, a range of occupational safety programmes have been established to protect workers (primarily in agriculture) from such effects. However, the clinical significance to veterans of the 1991 Gulf War is unclear because of the lack of any reported instances of acute cholinergic poisoning during that deployment. Gulf War veterans were apparently exposed at most to sub-clinical levels of OP cholinergic toxins such as pesticides and military nerve agents. For example, in the Khamisiyah sarin exposure modelling conducted by the US Department of Defense, the exposure levels used were developed to be completely protective of civilians, by setting them orders of magnitude smaller than that leading to acute toxicity.

Interestingly, the IOM committee also placed in the category of 'inadequate/insufficient evidence to determine whether an association exists' insecticides and solvents and peripheral neuropathy, Parkinson's disease, amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD). They noted the difficulty in studying the relationship between environmental exposures and neurological disease due to uncertainty in diagnoses, and long latencies associated with these illnesses, and problems with self reported exposure data. For example, although there are many epidemiological studies that attempted to evaluate associations between agricultural chemicals factors and Parkinson's disease, subjects often have difficulty recollecting which specific pesticides they may have been exposed to. The committee identified 6 case-controlled studies of Parkinson's disease, who were primarily agricultural or other pesticide workers. They reported conflicting results among the studies, and concluded that there is only 'inadequate/insufficient' evidence of an association between insecticide exposure and Parkinson's disease.

Similarly, with ALS and pesticide exposure, the IOM committee identified only a single peer-reviewed study (McGuire *et al.* 1997). They concluded that also the study provided 'evidence of a relationship,' but that possible selection bias resulting in an overestimate of an effect made it 'inadequate/insufficient' evidence of an association.

Finally, the committee reviewed the literature associating AD with pesticide exposure. They found several studies on the relationship between insecticides and AD,

which were either negative or not relevant to exposure among Gulf War veterans. Therefore, the committee concluded that there was again only 'inadequate/insufficient' evidence of an association between this disease and insecticide exposure.

(j) *Fuels and combustion products*

The third 'Gulf War & Health' IOM committee reviewed chronic health effects associated with exposure to oil-well fire combustion products, diesel-heater fumes, hydrogen sulphide (a specific oil-well fire product), hydrazines and red fuming nitric acid (as rocket propellants), and gasoline and jet fuel. Their 2004 report included nine positive findings linking certain long-term health effects with exposure to combustion products and rocket propellants (table 4). Most of studies supporting the committee's findings involved people living in urban areas who were routinely exposed to ordinary 'smog' from motor vehicles, stoves, heaters and other common sources of ambient and indoor air pollution. Other studies involved occupational exposure to engine exhaust, for example, among professional motor vehicle drivers. A few studies were of actual veterans of the 1991 Gulf War, based upon their exposure to burning oil-well fires in the Gulf War theatre.

As with earlier IOM reports, all positive findings were previously very well-documented associations between the generally commonplace environmental exposures and various specific diseases, with an abundant scientific health literature available for review. These include an association between combustion products (i.e. exhaust from engines 'smog,' oil-well-fire smoke, and fumes from tent heaters) and lung cancer, cancers of nasal cavity and nasopharynx, cancers of the oral cavity and oropharynx, laryngeal cancer, bladder cancer, low birth weight/intrauterine growth retardation and exposure during pregnancy, preterm birth and exposure during pregnancy, and asthma. They also reported an association between exposure to hydrazine rocket propellants and lung cancer, although according to reports from the US Department of Defense, these fuels were not used during the 1991 Gulf War.

Interestingly, the IOM committee reported no long-term health consequences from exposure to fuels. That is not to say the IOM did not identify certain acute and immediate health effects from exposure to such fuels. However, their review did not reveal any long-term effects that manifested only months or years after an acute poisoning from exposure to fuels.

(k) *Problems extrapolating to deployed military personnel*

There are always uncertainties extrapolating health effects observed among civilian workers and urban dwellers to health effects expected among deployed service members. The best epidemiologic studies on long-term health effects from combustion products and fuels are those of urban dwellers and workers exposed over years to decades. However, their relevance to health effects anticipated among military personnel serving in the relatively short 1991 Gulf War is not clear, since the exposures involved are typically much longer (e.g. years to entire lifetimes for urban dwellers and workers) or

much larger (e.g. based upon highly exposed industrial workers). Similarly, urban dwellers and workers with larger or longer exposures are more likely to develop a particular disease than people who experienced smaller or shorter exposures.

Thus, the IOM committee noted that reviewed studies primarily 'included people whose exposure was over a lifetime (as in community air pollution studies), or included workers employed in a particular industry over many years.' 'In contrast, the exposures experienced by veterans in the Persian Gulf were relatively short although the intensity might vary from occupational exposures,' and '[t]herefore, the exposures experienced in the gulf might only approximate exposures described in the occupational literature used in this report.'

(l) Gulf War exposure to combustion products

The 2004 IOM committee noted that poor exposure data for Gulf War veterans made it difficult to predict health effects from exposure to combustion products among this population. However, some relevant data on combustion product exposure is available from the US Department of Defense (DoD September 2000) investigations on exposures to oil-well-fire smoke and related combustion products during the 1991 Gulf War. From January through late February 1991, retreating Iraqi forces set fire to more than 600 Kuwaiti oil wells that lofted huge columns of smoke up into the atmosphere, and these oil-well fires were not completely extinguished until about 9 months later. Their report concludes that although the oil-well fires produced spectacular smoke plumes, the actual exposure to combustion products of US service members in that region was generally unremarkable. Furthermore, unlike many Gulf War environmental hazards of concern, an extensive monitoring effort by various agencies for air pollutants and combustion products from the 1991 Gulf oil-well fires is available to support firm conclusions about such exposure. Nevertheless, the DoD report also concludes that some individual veterans who were near the oil-well fires could have been exposed to high levels of large particulates, primarily as material deposited directly to skin or clothing rather than through inhalation.

The DoD report concludes, '[a]t the time of the destruction, the medical and environmental community feared exposure to the fires would result in catastrophic acute and chronic health effects. However, the fires' high combustion efficiency, the nature and amount of the smoke's contaminants, the lofting effect created by solar heating, and the local wind and weather conditions combined to reduce the fires' impact on military and civilian populations.' 'Results of air monitoring studies indicated, except for particulate matter, air contaminants were below levels established to protect the health of the general population. However, there were self-reports by a number of veterans who complained of acute symptoms they allege were a result of their proximity to the burning oil wells.'

The report also notes that exposures to US service members were quite short compared to civilians dwelling in US cities exposed to urban 'smog' and indoor air pollution, or workers exposed to engine exhaust. 'Fortunately, the time period during which military

and civilian populations were subjected to the fires' pollution was relatively short.' Although, '[w]hile smoke plumes occasionally touched the ground, enveloping nearby personnel, few were in those areas for extended periods of time.'

In an interesting comparison of deployment-related combustion product exposure, blood and urine samples from a group of US troops were collected before, during and after deployment to Kuwait during the 1991 Gulf War, the centre of the burning oil-well fires (US Army Environmental Hygiene Agency 1991). The concern was that troops stationed in Kuwait near the burning oil-well fires would be exposed to high levels of polyaromatic hydrocarbons (PAHs) and other pollutants. Samples were measured for volatile organic carbons (VOCs), PAH-DNA adducts, metals, and sister chromatid exchange frequency in lymphocytes. Surprisingly, this troop biomonitoring study found low PAH concentrations in Kuwait (Poirier *et al.* 1998). Biomonitoring with DNA adduct assays showed the lowest exposures to troops located in Kuwait, with significant increases among soldiers after they returned to Germany. Levels of metals, VOCs, and PAH-DNA adducts were essentially identical or showed decreases among troops while they were in Kuwait, compared to troops living in Germany. In particular, lead levels in blood were not statistically altered during deployment to the Gulf War theatre. 'Overall, the data suggest that this group of soldiers was not exposed to elevated levels of PAHs while deployed in Kuwait.'

(m) Gulf War exposure to hydrazine rocket propellants

According to another DoD investigation, rocket fuels used by Iraqi forces in Scuds and several smaller missiles during the 1991 Gulf War contained a type of kerosene and red fuming nitric acid (also known as IRFNA). They state that apparently Iraq had experimented with hydrazine rocket fuels including UDMH, however they concluded that these fuels were not used during that conflict. 'In addition to IRFNA, missile fuels were also potential battlefield hazards to coalition forces. The missile fuel that Iraq used in its older Soviet systems was a specially refined kerosene-like substance (called kerosene in the literature). Some improved missiles used UDMH in combination with IRFNA. The Soviet Union used UDMH in their Scuds, *but we have no evidence that Iraq used UDMH*' (emphasis added). Therefore, it appears unlikely that any Coalition service members were exposed to hydrazine rocket fuels during the 1991 Gulf War.

(n) Reproductive health effects among Gulf War veterans

Compared to previous IOM committees, the 2004 committee decided to focus greater attention on potential reproductive health effects (table 4). They noted that previous IOM reports on Gulf War veteran health focused primarily on health effects to adults, because pregnancies during the 1991 Gulf War were thought to be rare and pregnant women were thought to have been immediately evacuated from the Gulf War theatre. However, the committee described recent published data indicating that there were more

pregnancies than previously reported. Furthermore, pregnancies were typically not identified until 2 to 6 weeks after conception, and most pregnant service members would have been evacuated during the first 6 to 12 weeks of pregnancy. Therefore, the committee expanded its search of epidemiological literature to include reproductive health outcomes from exposures during the first trimester of pregnancy. The committee reported finding 'limited/suggestive' evidence of an association between exposure during pregnancy to hydrazine rocket fuel and low birth-weight, intrauterine growth retardation, and preterm birth. However, since Coalition forces were apparently unlikely to have been exposed to these agents during the 1991 Gulf War, the clinical significance of this finding is not clear. IOM committees have not found any other reproductive health effects to be associated with any other Gulf War risk factor they reviewed. This general topic is covered in greater detail in the contribution from Professor Doyle and colleagues (Doyle *et al.* 2006).

4. CONCLUSIONS, IMPACT OF THE IOM STUDIES AND LESSONS FOR THE FUTURE

Relying upon the independent and highly credible reviews by the IOM and similar groups from the UK of scientific and medical peer-reviewed literature remains an effective means for evaluating potential health effects from environmental hazards associated with service in the 1991 Gulf War. It allows VA to develop fair and scientifically-based healthcare and compensation policies for these veterans. Moreover, the scientific rigour and independence of the IOM makes their conclusions highly credible in the eyes of virtually all stakeholders.

Based on current IOM reports, VA has not made any special presumptions of service connection for any of the health effects connected to Gulf War environmental risk factors, although ALS has been linked to deployment in the first Gulf War in epidemiological studies. Following publication in 2003 of a paper showing a small but significant increased risk of ALS among veterans of the 1991 Gulf War (Horner *et al.* 2003), VA's Secretary announced that all Gulf War veterans diagnosed with that disease at that time would be granted service connection. Following the subsequent publication of a paper showing similar elevated risk of ALS among all US veterans of all eras, from World War 2 on (Weisskopf *et al.* 2005), VA has requested the IOM to review all the relevant scientific and medical evidence of an association between ALS and military service in general.

The IOM review process will continue with new risk factors and updates for previous reviews. For example, a recent publication (Bullman *et al.* 2005) reports that US Army 1991 Gulf War veterans possibly exposed to low levels of nerve agents during March 1991 weapons demolitions at Khamisiyah, Iraq, have an increased risk for brain cancer. However, limitations of the study include questions about the underlying exposure modelling, lack of biological plausibility (sarin and related compounds are not considered to be carcinogenic), and problems of chance findings from multiple comparisons. Despite calls to automatically service connect brain cancer among Gulf War veterans based

on this study, VA has elected to have the report reviewed by an IOM committee, to evaluate this new scientific evidence for a possible association between sarin exposure and brain cancer. This mechanism will provide a scientifically based and credible policy decision on this important topic.

The views expressed in this article are the author's and not necessarily those of the Department of Veterans Affairs.

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