



Specialist Medical Review Council

Declaration and Reasons for Decisions

Section 196W

Veterans' Entitlements Act 1986

Re: Statements of Principles Nos. 55 and 56 of 2014

in respect of Chronic Multisymptom Illness

Request for Review Declaration No. 33

1. In relation to the Repatriation Medical Authority (the RMA) Statements of Principles **Nos. 55 and 56 of 2014 concerning chronic multisymptom illness** made under subsections 196B of the Veterans' Entitlements Act 1986 (the VEA), the Council under subsection 196W(5) of the VEA:

DECLARES that there is insufficient sound medical-scientific evidence on which the RMA could have relied to amend the Statements of Principles to include the following factor(s):

- depleted uranium;
- oil well smoke;
- medical countermeasures (such as pyridostigmine bromide, and vaccinations for anthrax, plague, pertussis);
- contaminated food and water;
- chemical and biological weapons; and
- pesticide exposure (including N,N-diethyl-m-toluamide (DEET)).

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REASONS FOR DECISIONS

INTRODUCTION

1. The Specialist Medical Review Council (the Council) is an independent statutory body established by the VEA. In general terms, upon receipt of a valid application the Council is to review as relevant:
 - the contents of Statement/s of Principles in respect of a particular kind of injury, disease or death; or
 - a decision of the Repatriation Medical Authority (RMA) not to determine, not to amend, Statement/s of Principles in respect of a particular kind of injury, disease or death.
2. In conducting a review, the Council must review all of the information (and only that information) that was available to the RMA when it made the decision under review. This is information which was actually used by the RMA as opposed to information which was generally available but not accessed by the RMA. A list of the information that was available to the RMA is listed in **B1 of Appendix A**.
3. Fundamental to Statements of Principles (SoPs), and so to a Council review, is the concept of sound medical-scientific evidence (SMSE), as that term is defined in section 5AB(2) of the VEA.¹

¹ The sound medical-scientific evidence is a subset of the available information. It comprises those articles which the Council considers:

- a) are relevant to the matters within the proposed scope of review, and
- b) satisfy the definition in the VEA of 'sound medical-scientific evidence'.

Sound medical-scientific evidence is defined in section 5AB(2) of the VEA as follows:

"Information about a particular kind of injury, disease or death is taken to be 'sound medical-scientific evidence' if:

- a) the information:
 - (i) is consistent with material relating to medical-science that has been published in a medical or scientific publication and has been, in the opinion of the Repatriation Medical Authority, subjected to a peer review process; or
 - (ii) in accordance with generally accepted medical practice, would serve as the basis for the diagnosis and management of a medical condition; and
- b) in the case of information about how that kind of injury, disease or death may be caused – meets the applicable criteria for assessing causation currently applied in the field of epidemiology."

The latter requirement is held to mean 'appropriate to be taken into account by epidemiologists'.

4. The SMSE relevant to this application (the relevant SMSE) is listed in the reference list at the end of this document.
5. The information to which the Applicant referred, being information which the RMA advised was new information, that is, information which was not available to the RMA at the relevant times, was not considered by the Council in reaching its review decision is listed in **B2 of Appendix B**.
6. **Appendix A** sets out further details regarding the composition of the Council for this review and the legislation relating to the making of SoPs.

SCOPE OF THIS REVIEW

7. The Specialist Medical Review Council (SMRC) received an application seeking review of the contents of SoPs Nos. 55 and 56 of 2014 for chronic multisymptom illness. The Applicant (the Australian Gulf War Veterans' Association) contended that there was SMSE on which the RMA could have relied to amend either or both SoPs in respect to chronic multisymptom illness, and to include factors for:
 - Environmental hazards such as, depleted uranium, oil well smoke, medical countermeasures (such as pyridostigmine, and vaccinations for anthrax, plague, pertussis), contaminated food and water, chemical and biological weapons, and pesticide exposure (including N,N-diethyl-m-toluamide (DEET)).
8. The Council, when reviewing the SMSE, must determine whether or not there is SMSE on which the Authority could have relied to determine a SoPs under subsection 196B(2), or a SoPs under subsection 196B(3), in respect of that kind of injury, disease or death.
9. The Council, when reviewing the SMSE, must determine whether or not there is SMSE, which indicates a reasonable hypothesis connecting the particular injury, disease or death to the relevant service.
10. In a reasonable hypothesis, the evidence 'points to' as opposed to merely 'leaves open' a link between injury, disease or death and the relevant service. In a reasonable

hypothesis, the link is not 'obviously fanciful, impossible, incredible or not tenable or too remote or too tenuous'.²

11. If the Council is of the opinion that a reasonable hypothesis has been raised, the Council proceeds also to determine whether a connection exists to relevant service on the balance of probabilities,³ i.e. whether the connection is more probable than not.
12. In these Reasons, the association for both the reasonable hypothesis test and the balance of probabilities test are respectively referred to as the 'relevant association'.
13. The Council exercises its scientific judgement in weighing the evidence about the relevant association.

COUNCIL'S DECISION ON THE SCOPE OF REVIEW

14. The Council wrote to both the Applicant and the Repatriation Commission and the Military Rehabilitation and Compensation Commission (the Commissions) advising its decision on the proposed scope of the review and inviting comment. No comments were received on the proposed scope of the review and therefore the Council decided that it would have particular regard to whether there was SMSE on which the RMA could have relied to amend either or both of the SoPs in the following ways:

- A. amend either or both of the SoPs Nos. 55 and 56 for chronic multisymptom illness in the following ways:

the possible inclusion of a factor or factors as contended, for exposure to environmental hazards such as, depleted uranium, oil well smoke, medical countermeasures (such as pyridostigmine, and vaccinations for anthrax, plague, and pertussis), contaminated food and water, chemical and biological weapons, and pesticide exposure (including DEET).

² See the full Federal Court decision in *Repatriation Commission v Bey* (1997) 79 FCR 364 which cited with approval these comments from Veterans' Review Board in *Stacey* (unreported 26 June 1985), all of which were in turn cited with approval in the *Moore J* decision at [33].

³ Relevant service in balance of probabilities Statements of Principles refers to non-operational service having regard to the various definitions applying to types of 'service' as defined in the VEA and the Military Rehabilitation and Compensation Act 2004 (the MRCA).

METHODOLOGY (THE AVAILABLE INFORMATION)

15. The RMA provided the SMRC with a list of 819 papers that it advised were available to it when it last investigated the questions under review. Conclusions were based on an overall evaluation of the papers by the Council. Papers referenced in these Reasons are those that the Council considered were most relevant to the issues before it.
16. The RMA provided a list of papers found in the bibliography of the United States (US) Department of Veteran Affairs (VA) Research Advisory Committee on Gulf War Veterans' Illnesses chaired by Mr James H. Binns,¹ indicating over 1500 papers for which it extracted abstracts only. Many of these papers were in the list of available papers provided by the RMA, but there were also others that did not appear in the RMA's list. The Council reviewed this list to identify any papers that in its view were relevant to the review, and accessed those papers.

WRITTEN AND ORAL SUBMISSIONS

17. The Council took into account the submissions made to it, both written and in oral form.

Applicant

18. The Australian Gulf War Veterans' Association (The Applicant) made submissions to the SMRC on 27 March 2015 and 15 March 2016. The Applicant also asked the SMRC to note its detailed application to the RMA of 3 April 2013.
19. Representatives of the Applicant also made oral submissions complementing their written submission at the Council's meeting on 17 August 2016.
20. In summary, in respect to the medical science, the Applicant submitted that the chronic multisymptom illness SoPs do not go far enough, contending that the focus of the SoPs is limited to factors defined as psychological stressors. The Applicant contended that the current SoPs fail to provide for veterans for whom psychological stressors do not apply, and that the SoPs preclude or unnecessarily complicate steps for seeking medical treatment and/or compensation.
21. The Applicant contended that chronic multisymptom illness is associated with a combination of other factors in some veterans. The Applicant's contentions for each factor (e.g. for depleted uranium, oil well smoke, medical countermeasures (such as pyridostigmine and vaccinations), contaminated food and water, chemical and biological

weapons, and pesticide exposures) are summarised in the sections setting out the Council's analysis of the SMSE for each of the factors in scope for this review.

Criticism of the RMA

22. The Applicant was critical of the RMA's reliance on the Institute of Medicine (IOM)⁴ and contended that the RMA 'cherry-picked' the evidence saying, that there was less than five per cent of the 1400 papers the Research Advisory Committee on Gulf War Veterans' Illnesses (the RAC)⁵ (often referred to as the 'Binns report'¹) looked at, were included in the review.
23. The Applicant referred new papers to the SMRC, which are listed in **B2 of Appendix B**.

Commissions' Contentions

24. The Repatriation Commission and the Military Rehabilitation and Compensation Commission (the Commissions) made a written submission to the Council received on 17 March 2014. In the submission by the Commissions contended that chronic multisymptom illness:

- "does not have any specific pattern of symptoms or signs, nor pathognomonic features;"
- "does not have characteristics that enable it to be satisfactorily differentiated from normality nor established diseases;"
- "has not to date gained widespread recognition or acceptance in the general medical community; "and
- "does not have the necessary features to warrant designation as a disease."

25. The Commissions contended that chronic multisymptom illness "overlaps extensively with other unexplained symptom and psychiatric disorders" for example, chronic fatigue

⁴ The Institute of Medicine (the IOM) committees (now known as The National Academy of Medicine) have prepared the Gulf War and Health series of reports and have assessed the evidence for possible health effects associated with exposures experienced by veterans during the 1990-1991 Gulf War. The IOM reports to the US Department of Veterans' Affairs.

⁵ The Research Advisory Committee on Gulf War Veterans' Illnesses (the RAC) provides advice and makes recommendations to the Secretary of US Department of Veterans' Affairs on proposed research studies, plans, and strategies related to understanding and treating the health consequences of military service in the Southwest Asia theatre of operations during the 1990 - 1991 Gulf War.

syndrome, fibromyalgia, somatoform disorder, depressive disorders and other psychiatric disorders. They also contended that a diagnosis of chronic multisymptom illness is highly likely to result from “misattribution of symptoms that are better accounted for by other disease or injury, or a non-pathological explanation (e.g. lifestyle factors in the case of fatigue).”^{2(p6)}

26. The Commissions noted that when the RMA determined SoPs for chronic multisymptom illness, it based its case definition on the US Centers for Disease Control and Prevention (CDC) definition,³ restricting the SoP to the severe form of chronic multisymptom illness consistent with the CDC definition, and adding an exclusion criteria, noting that the CDC definition does not have exclusion criteria.
27. The Commissions contended that the CDC definition does not have any exclusion criteria for established medical or psychiatric illnesses that would account for some or all of the required symptoms.²
28. In response to the variations made to the CDC case definition for chronic multisymptom illness by the RMA, the Commissions observed:

The RMA, in considering whether to determine SOPs relating to unexplained symptom complexes in veterans, has evidently concluded that CMI as defined by the CDC is not a suitable condition to be the subject of SOPs and have formulated its own customised definition. It has restricted the SOP coverage to the severe form of CMI (as per the CDC definition), but also further restricted the SOP application by adding stipulations that:

The collection of symptoms relied upon to make the diagnosis is distressing and results in severe disruption of social and occupational functioning; and
Any or all of the symptoms are not better explained by another medical or psychiatric condition.

The RMA has indicated in its statement of reasons document that such stipulations are necessary to warrant designation of the condition as a disease. However, on the basis of professional advice that was available to the Commissions, these additions make the RMA definition of CMI unique, and, in consequence, the relevance of any available epidemiology concerning

symptom clusters in Gulf War veterans and others to the entity defined by the RMA becomes questionable.^{2(p6)}

29. The Commissions stated that they “do not wish to offer any view on whether the information that was available to the RMA on CMI warrants any amendment to the existing SoPs.”^{2(p6)}

COUNCIL'S DECISIONS ON THE RELEVANT SOUND MEDICAL-SCIENTIFIC EVIDENCE

30. The Council considered that the SMSE to be assessed in the review should comprise information:

- that was available to the RMA at the relevant times;
- which was sent by the RMA to the Council under section 196K of the VEA;
- which was considered by the Council to be SMSE as defined in section 5AB(2) of the VEA being information which:
 - a) epidemiologists would consider appropriate to take into account; and
 - b) in the Council's view 'touches on' (is relevant to) matters within the scope of review.

31. The Council's final decision on the SMSE for the review was that it should comprise the information listed in the reference list at the end of this document.

32. Information, which the RMA advised was not available to it at the relevant times was not taken into account by the Council for the purposes of the review, as it could only be considered as 'new information'.

Council's Evaluation of the Sound Medical-Scientific Evidence

33. When evaluating the SMSE, the Council focussed on information relevant to the scope of the review and the list is at **B1 of Appendix B**.

34. In forming its decisions on the SMSE, the Council brings to bear its scientific expertise and judgement. The Bradford Hill criteria and other tools or criteria appropriate to be taken into account by epidemiologists were applied to the papers as it considered appropriate.

35. The Council also considered any methodological limitations or flaws (including such things as statistical power, control of confounders, bias, exposure assessment methods etc.) in the various papers.
36. For ease of reference, the Bradford Hill criteria (noting that these are not exhaustive) are:
- strength of association
 - consistency across investigation
 - specificity of the association
 - temporal relationship of the association
 - biological gradient
 - biological plausibility
 - coherence
 - experiment
 - analogy
37. The Council notes that these criteria, apart from temporality, are not necessary conditions of a cause and effect relationship. They act to evaluate the evidence of such a relationship.
38. The Council noted that univariate analysis of data considers the effect of only one variable at a time, bivariate analysis considers the effect of two variables at a time, and in multivariate analysis more than two variables are simultaneously analysed. As multivariate analysis considers a number of variables together, the potential effects of confounding or interaction are more likely to be adequately assessed. Therefore, the Council paid particular attention to the SMSE that provided multivariate analysis.
39. The Council focussed its evaluation on those papers that provided data from which the Council could draw conclusions regarding chronic multisymptom illness.
40. The Council noted the Applicant made reference to animal studies in their submissions to the SMRC and the RMA. The Council considers that while animal studies may sometimes support the biological plausibility of an association, the results from animal studies may not be generalisable to humans. It considered animal studies are best used as initial research to generate hypotheses, which may indicate a need for further studies on human subjects or to demonstrate possible biological mechanisms. For this reason, the

Council focussed on studies that involved human subjects rather than animals for this review.

41. In discussing the factors in each section of these Reasons, the Council arranged the papers in order of study type, from the highest quality to the lowest quality (meta-analyses and systematic reviews; randomised controlled trials; cohort and case-control studies; cross-sectional studies; case reports and case series; and other studies. General (non-systematic) reviews of high quality were also included to provide an overview of the evidence and highlight important issues relevant to the review.

Council's Conclusions on the Relevant Sound Medical-Scientific Evidence

42. In reaching a decision about the existence or otherwise of a reasonable hypothesis, the Council must consider and evaluate all of the SMSE. In the situation where there is a single piece of evidence, such as a single study or paper, in support of a reasonable hypothesis, on its own that may or may not be enough to support the hypothesis. This information should be considered with other SMSE in identifying whether the SMSE indicates the relation to the medical condition. It was therefore important that the Council considered all information in context.
43. From the information that was available to the RMA at the relevant time, the Council considered all studies important to the scope of this review. In considering the matters within the scope of the review, the Council closely analysed these studies, both individually and collectively, taking into consideration both quantitative and qualitative evidence in its evaluations.
44. The Council, having closely analysed the available information, placed particular weight on the papers discussed in detail below, which it considered most salient to the questions. In its consideration of the SMSE, the Council looked for evidence of an association between chronic multisymptom illness and the contended factor. As defined in the SoPs, symptoms of chronic multisymptom illness include fatigue; mood-cognition: feeling depressed, difficulty remembering or concentrating, feeling moody, feeling anxious, trouble finding words or difficulty sleeping; or musculoskeletal: joint pain, joint stiffness or muscle pain. Thus, the Council paid careful attention to identifying studies that analysed these symptoms.

Council's Conclusions on Key Reviews, Reports and Studies

45. The Council noted that there are several important reviews, reports, and Australian-based studies cited throughout these Reasons that were available information, and made the following general observations.

IOM Reports

46. Since 1998, the IOM has issued a series of congressionally mandated reports on behalf of the US Department of Veterans' Affairs (VA) that have examined the scientific and medical literature on the potential health effects of exposures related to the 1990 - 1991 Gulf War. The IOM committees have published the Gulf War and Health series of reports, and between 2000 - 2016 ten reports have been published.⁴⁻¹³ The IOM committees have also published numerous other reports relevant to Gulf War and the Health of veterans including a number of updated reviews, of which several have been cited in these Reasons.¹⁴⁻¹⁷

47. IOM committees are scientific expert panels, whose members are selected based on their expertise and knowledge in the relevant area. The IOM committees scientifically review, evaluate, and summarise the peer-reviewed medical literature to determine the potential health effects of exposures and health.

48. The IOM was established in 1970 by the US National Academy of Sciences to secure the services of eminent members of appropriate professions to examine questions relating to policy matters pertaining to the health of the public. The Council noted that the IOM membership was composed of expert medical clinicians and medical scientists and was well-supported by dedicated staff. The IOM committee contacted representatives of veterans' organisations for advice in priority setting, but veterans who were not qualified as above did not sit on the committee.

49. For these reasons, the Council felt that findings presented in the IOM reports are in the large majority of cases, scientifically robust.

Research Advisory Committee on Gulf War Veterans' Illnesses (the RAC)

50. Established in 2002, the Research Advisory Committee on Gulf War Veterans' Illnesses (the RAC) is a congressionally-mandated body of physicians, scientists, and veterans that advises the Secretary of US Department of VA regarding Gulf War illness research. The

Chair of the committee, and several members, were not qualified in medicine or medical research. The RAC committee provided advice and made recommendations on proposed research studies, plans, and strategies related to understanding and treating the health consequences of military service in the Southwest Asia theatre of operations during the 1990 - 1991 Gulf War. Mr James H. Binns served as Chairman of the RAC Committee on Gulf War Veterans' Illnesses, a major report (often referred to as the Binns report¹) published by the RAC on Gulf War Illness and the Health of Gulf War Veterans in November 2008 and is cited throughout these Reasons.

51. The Council noted that the committee was not chaired by a medical scientist, and that several members of the committee were not medical scientists.
52. The Council noted that Binns et al¹ reported a number of significant associations calculated from reported data in the original studies, that were not reported by the primary authors. For example, Binns et al¹ calculated the crude odds ratios and confidence intervals from reported data in Table 4 of the Kang et al¹⁸ study for several exposures. Binns et al¹ reported significant (crude) associations between 'Gulf War-unique neurological symptom complex' and exposure to depleted uranium (odds ratio (OR) 5.7, 95% confidence interval (CI) 4.4-7.6)^{1(p405)}, food contaminated with oil smoke (OR 10.6, 95% CI 8.1-13.9),^{1(p411)} botulism vaccine (OR 3.5, 95% CI 2.7-4.7),^{1(p432)} ate food contaminated with smoke, oil (OR 10.6, 95% CI 8.1-13.9),^{1(p403)} bathed in or drank contaminated water (OR 6.3, 95% CI 4.9-8.1),^{1(p403)} and nerve gas (OR 15.1, 95% CI 11.6-19.7).^{1(p400)} The Council noted that only the crude analysis was presented and confounders such as other coincident exposures were not adjusted for.
53. The Council noted and strongly agreed with the comment in the Binns report^{1(executive summary, p5)} that, "The use of self-reported exposure information raises a number of concerns, most obviously in relation to recall bias. These concerns emphasize the importance of assessing findings across a broad spectrum of studies, rather than relying on results from individual studies".
54. The Council noted that the Binns report¹ made positive conclusions about some exposures and Gulf War Illness (e.g. for pyridostigmine and pesticide use) which were not supported by the findings of the IOM reports, and not supported by most papers in the medical literature more generally. The Council felt that the findings presented in the IOM

reports, being based on rigorous methodology and conducted entirely by qualified medical experts, were more robust than those of the Binns report.

Australian Gulf War Studies

55. The Australian Gulf War Veterans' Health Study (AGWVHS) was the first comprehensive health study of a group of Australian War veterans involved in a single theatre of war. The study has been conducted by a collaborative medical research team from the Department of Epidemiology and Preventive Medicine at Monash University, Health Services Australia, the University of Western Australia, and The Australian Centre for Post-traumatic Mental Health at the University of Melbourne. A series of studies investigating the health of Australian Gulf War veterans by Sim et al,¹⁹⁻²¹ Kelsall et al,²²⁻²⁵ and Glass et al²⁶ have been cited in these Reasons.

CHRONIC MULTISYMP TOM ILLNESS

Preliminary Comments

56. The Council noted that there is no universally agreed case definition for chronic multisymptom illness and that the term is applied differently by different researchers. However, in this review, the Council assessed the available information in respect to the definition of chronic multisymptom illness as set out in the SoPs.

57. In the SoPs Nos. 55 and 56 of 2014,²⁷ the RMA defined "chronic multisymptom illness" as:

...a condition characterised by multiple somatic symptoms which has been diagnosed by a specialist physician or a psychiatrist and which meets the following criteria:

- A. There are one or more current symptoms from two of the following three categories and at least one symptom in each of the categories must be rated as severe:
 - i. fatigue;
 - ii. mood-cognition: feeling depressed, difficulty remembering or concentrating, feeling moody, feeling anxious, trouble finding words or difficulty sleeping; or
 - iii. musculoskeletal: joint pain, joint stiffness or muscle pain; and

- B. The collection of symptoms relied upon to make the diagnosis is distressing and results in severe disruption of social and occupational functioning; and
- C. The collection of symptoms relied upon to make the diagnosis must have persisted for at least six consecutive months; and
- D. Any or all of the symptoms are not better explained by another medical or psychiatric condition.^{27(p1-2)}

58. The Council noted that different terms have been used in the SMSE, often interchangeably, to describe the chronic unexplained symptoms reported by veterans of the 1990 - 1991 Gulf War such as, 'Gulf War illness or syndrome', 'unexplained illness', 'medically unexplained symptoms' or 'medically unexplained physical symptoms', and 'chronic multisymptom illness'.^{12, 16} For this reason, this review included studies that have utilised a wide variety of terms to describe unexplained health symptoms (including all those listed above in this paragraph). However, the Council has focussed on those studies, which reported on symptoms of chronic multisymptom illness as defined in the SoPs. Where they were available, the Council also considered papers that reported exposure that was not specific to the Gulf War or to the military experience.

59. The next section sets out the Council's consideration of the SMSE in respect to each of the factors contended by the Applicant.

THE COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE NEW FACTOR(S) FOR:

DEPLETED URANIUM

Applicant's Contentions Concerning Depleted Uranium

60. The Applicant contended that the 1990 - 1991 Persian Gulf War was the first major conflict where depleted uranium munitions were deployed, but that records were not kept for exposure and dose.
61. The Applicant cited the RAC report by Binns et al¹ contending that many veterans took part in battlefield tours following the combat phase, entering tanks and other vehicles destroyed by depleted uranium munitions and potentially coming into contact with fine particulate dust contaminated by depleted uranium.

62. The Applicant cited a study by Spencer et al²⁸ of 1119 US Gulf War veterans, which it contended found depleted uranium exposure was linked to the risk for chronic multisymptom illness.
63. The Applicant also cited studies by Haley and Kurt²⁹ and Kang et al¹⁸ to support the contention that exposure to depleted uranium is associated with risks for 'Gulf War illness' and 'unique neurological symptom complex'.

The Council's Assessment of the Sound Medical-Scientific Evidence Concerning Depleted Uranium:

Background

64. Depleted uranium is a man-made by-product of the uranium enrichment process which is designed to make uranium suitable for use in nuclear reactors and nuclear weapons.^{4, 30} Depleted uranium has a much lower specific activity (14.8 mBq/p.g) than naturally occurring uranium isotopes – it is generally held to be approximately 40 percent less radiologically active. It is 65 percent denser than lead, has a high melting point in excess of 1000°C, and burns when fragmented.^{4, 30}
65. The properties of depleted uranium have led to its increasing adoption by military forces and in some commercial uses. It can be used as a counterweight or as ballast in aircraft and instruments such as gyroscopes, but more commonly is used as either defensive protective armour for tanks and similar armoured vehicles, and offensively as armour-piercing ammunition used by tanks, aircraft and ships.³⁰
66. The 1990 - 1991 Gulf War represented the first systematic use of depleted uranium weapons in combat.^{1, 31} However, there are limited measurements or records that exist to quantify the amount of depleted uranium Gulf War veterans were potentially exposed to. Also there is relatively little information available from epidemiologic studies concerning veterans exposed to depleted uranium and its possible link to chronic multisymptom illness.
67. From a human health perspective, depleted uranium can oxidise when burned either via fire or after making contact with armour.^{4, 32-34} There are three potential means of depleted uranium oxides entering a human: via inhalation of depleted uranium oxide dust or residues, via ingestion following hand-to-mouth contact or contamination of clothing, or via penetration of the body as shrapnel containing depleted uranium.^{4, 34}

68. To categorise potential exposure, the US Department of Defense Office of the Special Assistant for Gulf War Illnesses (OSAGWI)³⁴ identified three levels of exposure:

- Level I exposure occurred in or near combat vehicles when they were struck by depleted uranium rounds or when soldiers entered vehicles soon after the impact.
- Level II exposure occurred when soldiers and civilian employees worked on depleted uranium-contaminated vehicles or were involved in clean-up efforts of depleted uranium-contaminated areas.
- Level III exposure occurred when troops were downwind from burning depleted uranium ammunition, depleted uranium-contaminated vehicles (burning or otherwise), or when personnel entered depleted uranium-contaminated tanks.^{4, 34}

69. Depleted uranium has potential chemical and radiological health effects. Since depleted uranium has only about 60 percent of the radiological activity of naturally occurring uranium, the majority of putative health effects are due to its chemical toxicity, rather than any radiological effects. The organ most susceptible to the chemical toxicity effects of depleted uranium is the kidney.³⁰

70. While considerable research has been conducted over many years into the health effects of exposure to naturally-occurring uranium, particularly in workers involved in mining and processing of uranium ore, very little research has been done on the health effects of human exposure to depleted uranium. What research has been done concerning human exposure has largely been confined to studies of veterans of the 1990 - 1991 Gulf War.

71. In its review of the SMSE, the Council considered a series of depleted uranium surveillance studies^{31-33, 35-40} conducted since 1993 by Baltimore VA Medical Centre to be the most persuasive because they involved the follow-up of individuals for whom there were biological measures of exposure to depleted uranium. These studies involved monitoring a group of soldiers involved in "friendly fire" incidents. The incidents involved an estimated 100 US tank crew members and soldiers, who may have inhaled or ingested airborne depleted uranium particles, and or experienced wound contamination by depleted uranium.³³ Some of this group also sustained multiple tiny fragments of

depleted uranium scattered through muscle and soft tissue.³⁹ Up until 2011, 20 years since first exposure, 79 veterans were identified as being exposed to depleted uranium, and the majority of them have participated in this health surveillance program.³⁷ In 2011, a new participant was identified, increasing the number to 80 veterans exposed and included in the surveillance program.³¹ After almost twenty years since first exposure, no significant evidence of kidney or cellular toxicity, and no neurocognitive impairment, has been noted.³¹

Reports, Reviews and Meta-analyses

72. Of the available reports, reviews, and meta-analyses the Council considered the best evidence on exposure to depleted uranium was documented in reports by the IOM.^{4, 11, 41} The Council also paid particular attention to a RAC report by Binns et al,¹ a RAND report by Harley et al³⁰ and Environmental Exposure reports by OSAGWI.^{34, 42}
73. Genotoxicity has also been examined as a potential clinical health effect in Gulf War veterans exposed to depleted uranium. In the 2000 IOM Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines report by Fulco et al,⁴ the IOM committee studied the health outcomes of exposure to natural and processed uranium in workers at plants that processed uranium ore for use in weapons and nuclear reactors. The IOM committee concluded that there was inadequate/insufficient evidence to determine whether an association exists between uranium exposure and 14 health outcomes. Chronic multisymptom illness was not specifically assessed.
74. In the subsequent 2008 IOM Updated Literature Review on Depleted Uranium,⁴¹ the IOM committee concluded that there was “inadequate/insufficient evidence to determine whether an association exists between exposure to uranium and all the health outcomes examined,”^{41(p5)} which included a wide variety of malignant diseases, renal and respiratory disease, neurologic effects, reproductive and developmental effects, cardiac effects, genotoxicity, hematologic effects, immunologic effects and skeletal effects.⁴¹
75. In the 2010 IOM Volume 8: Update of Health Effects of Serving in the Gulf War report,¹¹ the IOM committee stated the “assessment of depleted uranium exposure, especially high exposure, is considered to be more accurate than assessment of exposure to most other agents because of the availability of biologic monitoring information.”^{11(p14)} In

general, the Council considered objective measures of exposure such as biologic monitoring were substantially more accurate than self-reported exposure.

76. A large review by the US RAC in 2008 by Binns et al,¹ (discussed at [50-54]) concluded that “there is little information from Gulf War or other human studies concerning chronic symptomatic illness in relation to depleted uranium or uranium exposure.”^{1(p8)} This review was particularly comprehensive, examining all of the reported potential factors that have been argued as contributing to ‘Gulf War illness’. It should be noted that chronic multisymptom illness was not the main focus of this review, and in many instances chronic multisymptom illness was used as another term for ‘Gulf War illness.’ This focus is a limitation as far as the work of Review Council was concerned. However, the main strength of this review was in its comprehensive assessment of the extant medical and scientific literature. However, the Council did note some limitations with this review as discussed at [50-54].
77. The authors noted that in deployments and conflicts after the Gulf War involving depleted uranium exposure, multisymptom illness has not been seen. Furthermore, the authors stated, “Almost no information is available that directly supports or refutes a possible association between uranium exposure and chronic symptom complexes that resemble Gulf War illness.”^{1(p89)} Additionally, the authors of this report noted that depleted uranium exposure in veterans is among the least reliably reported exposures, due to potentially uncertain first-hand knowledge at the time of the exposure.¹ Over and above the usual problems related to accurate recall of self-reported exposures during the Gulf War, military personnel were “frequently not aware of what depleted uranium was, when it was used, or if they had come into contact with it.”^{1(p96)} Consequently, results from studies that “simply asked veterans whether or not they were exposed to depleted uranium during deployment are highly questionable.”^{1(p96)} The authors noted that in the medical literature there are no reports of a multisymptom illness induced by occupational exposure to uranium. However, they also noted that there are no studies in the available literature that specifically assessed the occurrence of symptoms of chronic illness in populations exposed to uranium. This lack of available literature suggests that there was insufficient evidence of any link between depleted uranium exposure and chronic multisymptom illness. From a chronic multisymptom illness perspective, the

authors concluded that depleted uranium exposure was not likely to be a primary cause of illness.¹

78. In a 1999 report by Harley et al³⁰ for the RAND⁶ corporation the authors acknowledged that exposure to uranium and other heavy metals in large doses can cause adverse health problems. However, they concluded that large variations in exposure to radioactivity from natural uranium in the normal environment have not been linked to negative health effects associated with radiation; and no increased morbidity or frequency of end-stage renal disease was observed in relatively large occupational populations chronically exposed to natural uranium at concentrations above normal ambient ones. This report did not specifically address chronic multisymptom illness.

79. An Environmental Exposure Report of Depleted Uranium in the Gulf (II)³⁴ conducted by the OSAGWI⁷ in 2000 concluded that:

... that while DU could pose a chemical hazard at high doses, Gulf War veterans did not experience intakes high enough to affect their health. Furthermore, the available evidence indicates that due to DU's low- level radioactivity, adverse radiological health effects are not expected. The available scientific and medical evidence to date does not support claims that DU caused or is causing Gulf War veterans' illnesses.^{34(Section7, p2)}

80. The findings of the 2000 Environmental Exposure Report of Depleted Uranium in the Gulf (II)³⁴ were consistent with the findings of an earlier report conducted by the OSAGWI in 1998.⁴²

Cohort and Case-control Studies

81. The Council reviewed a study by Spencer et al,²⁸ which specifically examined chronic multisymptom illness and 'Gulf War illness' symptoms.

82. Spencer et al²⁸ conducted a population-based case-control study of US Gulf War veterans from Oregon and Washington. The first phase of the study involved a mail-based survey of exposures and symptoms, and the second phase involved a clinical evaluation of cases

⁶ The RAND Corporation is an American non-profit global policy think tank created in 1948 to offer research and analysis to the US Armed Forces.

⁷ The Office of the Special Assistant for Gulf War Illnesses (OSAGWI) was established to investigate Gulf War veteran's unexplained illnesses and reports to the US Department of Defense.

and controls drawn from the survey responders. The clinical evaluation was comprehensive, including neurobehavioral and psychological testing. A large number of potential exposure factors were considered in their analysis. The self-reported risk factor exposures were compared in 241 veterans who met criteria for 'unexplained illness' (Gulf War unexplained illness' - Portland Environmental Hazards Research Centre (PEHRC) – defined and 'Gulf War illness' - CDC - defined chronic multisymptom illness) and 113 healthy controls. The authors concluded that the greatest risk factors for 'unexplained illness' were exposure to the sun, combat conditions, and the presence of medical conditions for which medical attention was sought while deployed.

83. The use of objective clinical evaluation was considered by the Council to be a methodological strength of this study in terms of its general approach to the research question. In addition, the population surveyed was quite diverse, covering all branches of the military (active and reserve) and a range of work activities during the deployment. However, the study had some limitations, including a low response rate of 55% for all surveys, poorly defined exposure criteria, potential recall bias due to self-reporting, as well as a lack of specific information on the symptoms experienced by those seeking medical help during the deployment. Overall, the Council found this to be a generally helpful study, albeit one which relied on self-reported exposures, which are a methodological limitation.
84. In terms of depleted uranium, this factor was combined into a generalised set of risk factors associated with combat conditions. The analysis showed that the odds ratio for the association with self-reported exposure to depleted uranium was 3.69 (95% CI 1.54-8.81) for 'Gulf War unexplained illness' (PEHRC-defined) and 4.46 (95% CI 1.74-11.4) for 'Gulf War illness' (CDC-defined). However, this apparently high odds ratio needs to be considered in the context of the limitations of this study specific to depleted uranium. The study relied on self-reports of depleted uranium exposure, which the authors found had the lowest test-retest reliability of all factors considered in this study. This finding indicates that true exposure to depleted uranium was likely to be poorly measured by self-report. Furthermore, there were no direct measures of depleted uranium exposure, and the study did not report the level of any actual exposure to depleted uranium.²⁸ The authors concluded that exposure to combat conditions was one of many general risk factors for self-reported illness in veterans. However, the study drew no specific

conclusions on the risks for depleted uranium on its own. The study's results therefore do not provide strong evidence of any association between depleted uranium and symptoms of fatigue, mood-cognition disorders or musculoskeletal issues consistent with chronic multisymptom illness.

Cross-sectional Studies

85. The Council reviewed a study by Kang et al,¹⁸ which specifically examined 'Gulf War illness' symptoms.
86. A cross-sectional study by Kang et al¹⁸ used exploratory factor analysis applied to the 47-symptom correlation matrix to identify a symptom syndrome specific to US Gulf War veterans of 10 423 Gulf War and 8960 non-Gulf War veterans. The authors found that Gulf War veterans with a cluster of symptoms consistent with 'neurological impairment' (blurred vision, loss of balance/dizziness, tremors/shaking, and speech difficulty) reported exposure to risk factors such as depleted uranium (among a large group of other exposures) at rates three or more times higher than non-veterans. Specifically, they reported that self-reported depleted uranium exposure was present in 28.9% of cases and 6.6% of controls. This finding in and of itself is not particularly strong. The authors, while stating that the results show evidence of a possible deployment syndrome, did not present any other statistical analysis, such as odds ratios. The study has significant limitations. It presents little actual data, no real statistical analysis, and relies on self-reported exposures with the inherent significant potential for recall bias. The authors themselves acknowledged the limitations of this study, and noted that objective clinical evidence is required to support their findings.
87. The Council also reviewed two studies of the AGWVHS by Sim et al¹⁹⁻²¹ and Kelsall et al,²² which examined reported exposure to depleted uranium and number of symptoms and health outcomes. Sim et al¹⁹⁻²¹ (discussed at [55]) included baseline data of the entire cohort of Australia's 1871 Gulf War veterans and a comparison group of 2924 Australian Defence Force (ADF), or formerly ADF personnel who had been in operational units at the time of the 1990 – 1991 Gulf War but who had not deployed to that conflict. The response rate was 81% for Gulf War veterans and 57% in the control group. No significant associations were found between exposure to 'depleted uranium shell casings' and the number of self-reported health symptoms, the Short-Form-12 (SF-12) physical

health measure, and functional impairment in Gulf War veterans.²⁰ In the Council's view, a strength of these studies is that they documented a measure of likely actual exposure to depleted uranium.

88. Kelsall et al²² (discussed at [55]) investigated the relationship between self-reported exposures and total number of symptoms of 1456 Australian Gulf War veterans and a comparison group of 1588 who were in operational units at the time of the 1990 – 1991 Gulf War, but were not deployed to that conflict. A postal questionnaire was administered and a comprehensive health assessment was carried out by doctors, nurses, and psychologists. Health symptoms were measured using the 63 item self-report symptom questionnaire that asked about the occurrence of symptoms in the month prior, and whether the severity of those symptoms were mild, moderate, or severe. Possible exposure to depleted uranium was defined by whether the veteran was 'in Camp Doha, Kuwait when the tank compound caught fire' or 'was involved in the subsequent clean-up operations', or 'if they reported either using depleted uranium munitions' or had 'entered or inspected destroyed enemy equipment' and 'had been in either Kuwait or in the battle zone areas'. The authors concluded that there was no association between the number of symptoms and possible exposure to depleted uranium, with a mean of 14.7 symptoms reported by those not exposed to depleted uranium and 14.2 symptoms in those exposed to depleted uranium. In the Council's view, this study had a number of methodological strengths, such as the relatively specific measurement of exposure to depleted uranium, and the objective clinical assessments made. The Council did note the self-reported nature of the survey data as a limitation.

Studies of People with Biological Measures of Depleted Uranium Exposure

89. A number of cohort studies^{31-33, 35-40} were conducted of US male Gulf War veterans who were exposed to depleted uranium during friendly fire incidents in 1991 enrolled in a long-term health surveillance program at the Baltimore VA Medical Centre. Uniquely, this series of studies used a biological measure of depleted uranium exposure, based on urine uranium levels. The use of a biological measure overcomes the very substantial issue of lack of objective exposure measure that is present in studies, which have only self-reported data. Chronic multisymptom illness was not assessed in any of these papers^{31-33, 35-40} however, a number of clinical assessments were conducted such as neurocognitive,

psychiatric, bone metabolism, reproductive health, genotoxicity, immunologic and renal function.

90. In a study more than seven years after exposure, McDiarmid et al⁴⁰ conducted a follow-up of the medical history and examination on 29 exposed Gulf War veterans and 38 non-exposed Gulf War veterans. Depleted uranium exposed veterans were still exhibiting high urinary uranium concentrations (range 0.01-30.7 µg/g creatinine compared to 0.01-0.05 µg/g creatinine in the non-exposed), but no clinical evidence of renal disease or other health effects. Neurocognitive testing revealed some subtle changes, including an association between urinary uranium levels and poorer performance on certain test batteries. However, the authors noted that there were only a small number of participants with elevated urinary uranium levels, and that a few participants with complex medical and clinical histories had contributed to much of the observed variance in performance.
91. In a study eight years after exposure, McDiarmid et al³⁹ studied 50 Gulf War veterans (29 veterans were seen for the first time and 21 were seen on other surveillance visits). The veterans underwent a large number of biological tests, and results of over 35 tests were reported in this paper, and thus it is possible that some significant findings may have arisen through chance. The study reported a statistically significant correlation between the rate of certain mutation indices in specific white cells and urine uranium levels. The authors noted that this finding did not translate into significant health effects and attributed these findings to the chemically toxic nature of depleted uranium rather than its radiological activity.³⁹ A further follow-up at the 10-year point by McDiarmid et al³⁸ confirmed these findings, with no clinical disease being evident in the 39 Gulf War veterans exposed to depleted uranium during friendly fire incidents examined (31 veterans had been seen previously on at least one occasion and 8 were examined for the first time).
92. McDiarmid et al³³ studied 32 Gulf War veterans' clinical laboratory parameters and urine uranium concentrations. All of these participants had been seen previously on at least one other occasion. Data were examined by stratifying the cohort into low uranium group (<0.10 µg/g creatinine) compared to high uranium group (≥0.10 µg/g creatinine), and uranium concentrations ranged from 0.001 µg/g creatinine to 41.8 µg/g creatinine. There were no clinically significant differences in laboratory parameters between the low

and high uranium groups. After 12 years, Gulf War veterans with depleted uranium fragments continue to excrete elevated concentrations of uranium in urine. No clinically significant uranium related health effects were observed in blood count, blood chemistries including renal markers, neuropsychological measures, and semen quality or genotoxicity measures.

93. McDiarmid et al³² reported an updated study of 34 Gulf War veterans who were previously assessed in 2005 (except for four veterans). Current uranium exposure was measured by urine uranium concentration at the time of their surveillance visit and cumulative uranium exposure was also calculated based on each veteran's past urine uranium concentrations since first exposure in 1991. Using either exposure metric (urine uranium concentration or cumulative uranium) results continued to show no evidence of clinically significant depleted uranium-related health effects. The authors concluded that evidence of a weak cytogenetic effect was shown, but that significant health effects arising from this effect were not seen.³²
94. McDiarmid et al³⁷ conducted a follow-up study of a cohort of 35 Gulf War veterans, 18 years after first exposure to depleted uranium (2 veterans were seen for the first time and 33 were seen on several previous biennial surveillance visits). Clinical evaluation, laboratory studies and urine samples were assessed. The authors stated that urine uranium excretion remained above normal in participants with embedded depleted uranium fragments (ranging from 0.006 to 1.88 µg U/g creatinine). No apparent evidence of renal functional changes or cellular toxicity related to uranium body burden and no marked differences in markers of bone formation or bone resorption were observed. However, the authors observed a statistically significant decrease in levels of serum intact parathyroid hormone and significant increases in urinary calcium and sodium excretion were seen in the high versus the low urine uranium groups. The authors stated that 18 years after first exposure, members of this cohort with embedded depleted uranium fragments continued to excrete elevated concentrations of urine uranium. The authors concluded there was no significant evidence of clinically important changes observed in kidney or bone, the two principal target organs of uranium.
95. In a study by Bakhmutsky et al³⁵ assessing genotoxic effects in Gulf War veterans exposed to depleted uranium as a function of uranium body burden, the levels of urine uranium were used to categorise the cohort into low and high exposure groups. Blood and urine

samples were collected from 35 (of 79) veterans enrolled in a long-term health surveillance program at the Baltimore VA Medical Centre. Participants were divided into two exposure groups, low and high, based on their mean urine uranium concentrations. The authors concluded there was no significant increase in cytogenetic changes in Gulf War veterans with long-term embedded depleted uranium fragments compared with Gulf War veterans with a normal uranium body burden.³⁵ A follow-up study³⁶ by the same authors in 2013 reached the same conclusions. The authors noted that chronic exposure to depleted uranium has not been seen to induce any degree of significant chromosome damage in exposed veterans.³⁶

96. A study by Hines et al³¹ examined 37 (of 80) Gulf War veterans who sustained inhalational exposure to depleted uranium during friendly fire incidents in 1991, enrolled in a long-term health surveillance program at the Baltimore VA Medical Centre for evidence of pulmonary health effects. No pulmonary health effects were seen, pulmonary function of the affected cohort was within the normal clinical range, and that inhalational levels of depleted uranium did not appear to cause long-term pulmonary health effects.

Council's Conclusions on Studies concerning Depleted Uranium:

Overall Quality of the Available Sound Medical-Scientific Evidence

97. In its review of the SMSE, the Council considered a series of cohort studies^{31-33, 35-40} conducted at the Baltimore VA Medical Centre since 1993, in which there were biological measures of depleted uranium exposure, provided the highest-quality data on the health effects of depleted uranium exposure. These studies typically show that veterans of the Gulf War with embedded depleted uranium shrapnel fragments have persistently elevated levels of urinary uranium. These increased urinary levels of uranium remain so over a decade since exposure to depleted uranium occurred. However, these elevated levels of uranium in the urine were not associated with any clinically significant health effects, including in the kidneys or bones.^{32, 33, 37, 39} Although the findings have been consistent over time, the authors did indicate that ongoing surveillance was needed. These cohort studies^{32, 33, 37-40} have not revealed any adverse clinical health outcomes or long-term health effects as a result of exposure to depleted uranium. Nor were cytogenetic abnormalities in peripheral blood lymphocytes³⁵ or long-term adverse

pulmonary health effects observed.³¹ No evidence of the clinical symptomatology typical of chronic multisymptom illness was reported during the study periods.

98. The cohort reports from the Baltimore VA group had long-term and consistent follow-up. They used an objective measurement of depleted uranium exposure, which adds to the strength of these studies, however, the sample was small. In addition, the selection of the urinary-uranium cut point of 0.10 µg/g of creatinine was not based on a generally accepted standard for urinary uranium.⁴¹ Overall, the Council considered these cohort studies to represent the most informative studies on exposure to depleted uranium, as biological measures of depleted uranium exposure were used.
99. There have only been a small number of studies conducted in Gulf War veterans that have been exposed to depleted uranium. However, only one study, by Spencer et al,²⁸ examined exposure to depleted uranium and 'Gulf War illness' using the CDC definition for chronic multisymptom illness. Even though the study by Spencer et al²⁸ demonstrated a significant association for combat conditions, which included exposure to depleted uranium in veterans self-reporting potential exposure, this study did not document or measure the level of any actual exposure to depleted uranium. As such, the Council felt that the reliance on self-reported exposure could have introduced a degree of recall bias, making interpretation of the results problematic. A study by Kang et al¹⁸ reported that Gulf War veterans with the 'neurological symptom complex' reported exposure to risk factors such as depleted uranium (among a large group of other exposures) at increased rates than non-veterans. However, the authors did not present any meaningful statistical analysis, which renders the association unclear. The Council considered that these papers were less convincing due to the numerous methodological issues outlined above.
100. Other studies examined exposure to depleted uranium and increased symptom reporting¹⁹⁻²² and reported no significant associations between depleted uranium and a number of health outcomes. Importantly, a number of comprehensive reviews^{1, 4, 11, 30, 34, 41, 42} have been conducted by various expert committees and these have also not found an association between exposure to depleted uranium and chronic multisymptom illness.

Summary

101. The available evidence on exposure to depleted uranium and health effects is limited, particularly in relation to chronic multisymptom illness. The long-term cohort studies on veterans with documented exposure to depleted uranium have not shown any evidence of long-term health effects. Therefore, the weight of the available evidence does not support an association between exposure to depleted uranium and the development of symptoms of chronic multisymptom illness.

THE COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE FACTOR(S) FOR DEPLETED URANIUM

102. In summary, based on the criteria described above at [34-37], the Council considered that the SMSE was insufficient to point to a link between chronic multisymptom illness and exposure to depleted uranium. On that basis, the SMSE does not indicate a reasonable hypothesis connecting chronic multisymptom illness to depleted uranium. As the Council has concluded that the reasonable hypothesis test was not established, the balance of probabilities test necessarily could not be met.

OIL WELL SMOKE

Applicant's Contentions Concerning Oil Well Smoke

103. The Applicant contended that burning oil wells caused widespread environmental contamination during the Gulf War, and cited a RAND report by Spektor⁴³ that veterans' health concerns are associated with exposures to, "...volatile organic compounds such as Benzene, Toluene [*sic*] and Xylene or exposures to polycyclic aromatic hydrocarbons including acidic aerosols, ultrafine particles and particulate matter (PM₁₀) which can comprise a group of compounds produced from the incomplete combustion of several carbon based substances."

104. The Applicant cited Unwin et al,^{44(p175, Table9)} Spencer et al,²⁸ and Wolfe et al⁴⁵ who they contended found evidence for an association between exposure to oil well smoke and chronic multisymptom illness.

105. The Applicant contended that Spencer et al²⁸ in a study of 1119 US Gulf War veterans found risks associated with spending 1-5 days exposed to oil well smoke and Wolfe et al⁴⁵

found that being in a position to be able to smell oil well smoke also showed evidence for risks associated with chronic multisymptom illness.

106. The Applicant cited studies by Haley and Kurt,²⁹ Gray et al,^{46(p1040-41, Table7)} and Spencer et al²⁸ to support the contention that exposure to oil well smoke was associated with risks for 'Gulf War illness'. The Applicant cited Kang et al¹⁸ to support the contention that exposure to oil well smoke was associated with risks for "unique neurological symptom complex".

107. The Applicant contended that a study by Gray et al^{46(p1040-41, Table7)} of 3831 US Gulf War veterans exposed to oil well smoke had an increased risk of study-defined 'Gulf War illness'.

108. The Applicant contended that a study by Cherry et al^{47(p303, Table 4)} of 7791 United Kingdom (UK) Gulf War veterans found the overall symptom severity was associated with the number of days exposed to oil well smoke and this was statistically significant.

The Council's Assessment of the Sound Medical-Scientific Evidence Concerning Oil Well Smoke:

Background

109. In early 1991, retreating Iraqi forces set fire to more than 600 oil wells. Fires burned until November 1991, potentially exposing thousands of military personnel to combustion products.⁶ Veterans were probably exposed to air pollution as smoke plumes rose and combined to form giant plumes that could be seen for hundreds of kilometres.⁶ Oil well smoke was a very visible aspect of the 1990 – 1991 Gulf War. Observation of smoke was considered to be a distinguishing feature of the Gulf War compared to other Australian deployments, with the majority of Australia veterans reporting this occurrence.^{23, 26}

Reports, Reviews and Meta-analyses

110. Of the available reports, reviews, and meta-analyses the Council considered the best evidence on exposure to smoke from oil well fires was documented in reports by the IOM^{6, 11} and a RAND report by Spektor.⁴³

111. The 2005 IOM Volume 3: Fuels, Combustion Products, and Propellants report⁶ the IOM committee concluded that there was inadequate/insufficient evidence for neurologic effects from exposure to fuels and combustion products. The IOM committee found that:

Several population-based Gulf War studies found a relationship between veterans self-reported fuel exposure and their self-reported neuropsychologic or cognitive symptoms or non-specific symptoms.^{28, 44, 48, 49} However, because of recall bias, the committee considered them as providing weak evidence of a relationship.⁵⁰... The studies from the Gulf War provide weak evidence of a relationship between fuel exposure and neurobehavioral effects.^{6 (p321)}

112. In the 2010 IOM Volume 8: Update of Health Effects of Serving in the Gulf War report,¹¹ the IOM committee noted that only self-reported exposure to oil well fires was linked to an increase in self-reported respiratory symptoms that were suggestive of asthma and bronchitis. However, the Council noted that respiratory symptoms are not recognised as symptoms of chronic multisymptom illness.

113. In a 1998 RAND report, Spektor⁴³ reviewed the scientific literature on possible health effects due to exposures to the Kuwait oil well fires. The review reported that ground levels of volatile organic compounds were low (except during inversion episodes), based on eight ground level monitoring sites, and thousands of samples from May-December 1991.⁴³ Other monitoring in an earlier period (March) by the US Environment Protection Agency confirmed the Environment Health Agency findings reported by Spektor.⁴³ The author concluded that:

The health surveys conducted during the oil fires indicate increased symptoms and an association between prevalence of complaints and proximity to the oil fires. As yet, there are no data to support those symptoms being indicators of disease or that the symptoms were associated with proximity to oil fires.^{43 (Ch4, p1)}

Cohort and Case-control Studies

114. The Council reviewed studies by Powell et al,⁵¹ Steele et al,⁵² Spencer et al,²⁸ and Lucas et al,⁵³ which specifically examined chronic multisymptom illness or 'Gulf War illness' symptoms.

115. In a cohort study by Powell et al⁵¹ the relationship between self-reported chronic multisymptom illness (CDC-defined) and possible exposure to an open-air burn pit at three bases among US veterans deployed to operations in Iraq and Afghanistan after 2001 was investigated. Exposure was measured by a history of deployment to an area

within three miles of a documented burn pit. There were 21 400 study participants, 3578 (exposed deployment) were identified with at least one deployment to an area within three miles of a documented burn pit and 17 822 (other deployment). After adjustment for multiple confounders, the authors concluded that these data did not provide evidence for an association between burn pit exposure and subsequent short-term development of chronic multisymptom illness. A small subgroup of 282 people with prolonged exposure (>209 days) did appear to have a small statistically significant increase in risk of chronic multisymptom illness (Adjusted (Adj.) OR 1.19, 95% CI 1.02-1.40). Further follow-up was recommended. The authors concluded that, though strengthened by a large sample but limited by potential misclassification of exposure, these data suggested that deployers exposed to a burn pit were not at overall elevated risk of chronic multisymptom illness. Additionally, there was no indication that a particular camp was more likely associated with increased reporting of chronic multisymptom illness symptoms than another camp. The Council found that a strength of this study was the lack of reliance on self-reported exposure, giving the results more objectivity.

116. Steele et al⁵² compared self-reported wartime experiences in a population-based sample of 304 US Gulf War veterans. The study population involved 144 cases who met pre-established criteria for 'Gulf War illness' (Kansas-defined and CDC-defined chronic multisymptom illness) and 160 controls. The Kansas definition requires multiple and/or moderate-to-severe chronic symptoms in at least three of six defined symptom domains; fatigue/ sleep problems, somatic pain, neurologic/cognitive/mood symptoms, gastrointestinal symptoms, respiratory symptoms and skin abnormalities. The study examined a number of potential exposures. In general terms, the authors concluded that the aetiology of 'Gulf War illness' was complex and likely involved several deployment-related exposures whose relative contributions to 'Gulf War illness' differed in identifiable veteran subgroups.

117. Relative strengths of the Steele et al study⁵² were that it looked at a specific population of veterans in a geographic area, and had reasonably good total sample numbers. However, the authors highlighted a number of methodological limitations, which the Council agreed with. These included low actual subject numbers in many of the factors being examined, potential recall bias due to self-reporting of deployment exposures, and

its reliance on self-reported symptoms. Unlike the study by Spencer et al²⁸ discussed at [82], the Steele et al study⁵² did not make use of objective clinical assessments. Overall, the Council did not rely heavily on this paper due to the number of methodological issues.

118. In terms of oil well smoke, the authors found that there was very limited evidence of an association between 'Gulf War illness' and exposure to oil well smoke.⁵²

119. Spencer et al²⁸ analysed self-reported exposures and their association with 'Gulf War unexplained illness' (PEHRC-defined and CDC-defined chronic multisymptom illness) of US Gulf War veterans (discussed at [82]). In the univariate analysis, the odds ratios were significant for the association between self-reported eye irritation from burning oil well exposure: 1-5 days (OR 2.09, 95% CI 1.15-3.80) and 6+ days (OR 3.42, 95% CI 1.70-6.88) and 'Gulf War unexplained illness' (PEHRC-defined); and 1-5 days (OR 2.64, 95% CI 1.34-5.20) and 6+ days (OR 4.47, 95% CI 2.07-9.63) and 'Gulf War illness' (CDC-defined). However, the authors concluded that in the analysis controlling for multiple simultaneous exposures during the Gulf War, there was no significant association between the likelihood of having 'Gulf War unexplained illness' and self-reported exposure to oil well fires. The Council noted the study's methodological limitations (discussed at [82]).

120. Lucas et al⁵³ conducted a case-control study of 49 US Gulf War veterans with early-onset 'Gulf War illness' (cases) and 44 healthy Gulf War veterans (controls) matched on age, race, gender, rank during the conflict period, branch of service, and type of service. Veterans completed questionnaires about wartime exposures and early onset fatigue. 'Gulf War illness' (Lucas-defined) cases were defined as veterans who had persistent, unexplained fatigue and had two of the following unexplained symptoms for at least six months since their fatigue onset: cognitive difficulties, headaches, joint aches without swelling, muscle aches, unrefreshing sleep, or post exertional fatigue. Associations were presented for more than 30 war time exposures, and the association with 'Gulf War illness' was significant for 11 of these exposures. The authors found a significant association between 'Gulf War illness' and self-reported exposure to oil well fire smoke. There was a statistically significant association with exposure to oil well fire smoke (OR 8.54, 95% CI 2.41-37.52). The Council noted that in this study, subjects were recruited nationally, which might have reduced a cohort or regional bias, however, participants

were recruited through advertisements and articles that potentially introduced selection bias. The study also involved very small subject numbers. Exposure to oil well fire smoke was based on self-reporting, which has its methodological issues, and because of the small sample size, the authors stated they did not adjust for multiple comparisons and may not have been able to detect some exposure-health associations. The Council noted that the study did not focus on chronic multisymptom illness exclusively in order to capture many syndromes with fatigue as a symptom, which may or may not have reached criteria for any accepted definition of chronic multisymptom illness. Consequently, it was not clear how many people with chronic multisymptom illness were included in this study.

121. In a large cohort study by Smith et al⁵⁴ post-war hospitalisation rates of US military personnel exposed to smoke from the 1991 Kuwaiti oil well fires were compared with those of unexposed personnel. Exposures to particulate matter from oil well fire smoke were not based on self-report, but on integration of meteorologic data, diffusion modelling, and troop location data. The authors attempted to estimate total dose and identify a possible dose-response relationship by combining data on exposure concentration with data on duration of exposure and created a single variable for each veteran based on average daily exposure and length of exposure in days. No data were available on outpatient conditions, and this study did not address chronic multisymptom illness directly. The authors found no evidence of a dose-response relationship between smoke exposure and hospitalisation. The authors concluded that these data do not support the hypothesis that Gulf War veterans have an increased risk of post-war morbidity from exposure to Kuwaiti oil well fire smoke. The Council considered that strengths of this study were its population size, and its reliance on hospitalisation data, rather than on self-report.

Cross-sectional Studies

122. The Council reviewed studies by Unwin et al,⁴⁴ Wolfe et al,⁴⁵ Gray et al⁴⁶ and Haley and Kurt,²⁹ which specifically examined chronic multisymptom illness or 'Gulf War illness' symptoms.

123. Unwin et al⁴⁴ conducted a cross-sectional postal survey (self-report) on a random sample of UK Gulf War veterans (Gulf War cohort = 4248) and, stratified for age and rank,

servicemen deployed to the Bosnia conflict (Bosnia cohort = 4250) and those serving during the Gulf War but not deployed there (Era cohort = 4246). They used the CDC-defined chronic multisymptom illness definition in their study. Associations between the 15 most commonly self-reported exposures were examined, and a statistically significant association for 14 of the 15 exposures was found. The strongest association was for self-reported chronic fatigue syndrome. Most of the associations found were based on self-reported perception of health, with physical functioning demonstrating no statistically significant differences between the three cohorts.

124. The Unwin study targeted the cohort numbers above, but only had a response rate of 65% to the mail out. The final cohort numbers were: Gulf War cohort = 2735 (64%), Bosnia cohort = 2184 (51%) and Era cohort = 2422 (57%). The Council noted that the limitations of this study included the reliance on self-reported exposures, no objective evidence of either clinical symptoms or actual exposures, and difficulties in controlling for confounders and multiple exposures.

125. In terms of oil well smoke, self-reported exposure to smoke from oil well fires differed substantially between the three cohorts, 72.4% for the Gulf War cohort compared to only 3.9% for the Bosnia cohort and 3.1% for the Era cohort. Weak significant associations between chronic multisymptom illness and self-reported exposure to smoke from oil well fires were shown for the Gulf War cohort (OR 1.8, 95% CI 1.5-2.1) and the Era cohort (OR 1.8, 95% CI 1.1-2.9) but not for the Bosnia cohort (OR 1.4, 95% CI 0.8-2.3). The authors concluded that since associations of ill health with adverse events and exposures were found in all cohorts (and in two of the three cohorts for oil well smoke), they may not be unique and causally implicated in Gulf-War-related illness. The Council noted that the associations found were weak, if present at all, and made somewhat problematic by the significant limitations of the study.

126. Wolfe et al⁴⁵ in a cross-sectional survey of individual characteristics and self-reported exposures and health effects, examined the prevalence of symptoms and exposures identified as potential risk factors for 'multisymptom illness' (CDC-defined) among a group of US Army Gulf War veterans. Sixty percent of the respondents met the criteria for 'multisymptom illness' (CDC-defined). Of the 945 with complete data, 567 veterans met the criteria for 'multisymptom illness' (286 mild to moderate and 281 severe).

127. The Council noted that there were some methodological weaknesses in this study. The authors used a cross-sectional study design, the use of retrospective self-reported exposures and the use of non-standardised questions, which potentially introduced recall bias. There were also relatively low response rates and the potential for non-response bias. The most significant weakness was the reliance on self-reported exposures and symptoms.

128. In terms of oil well smoke, 62.5% of all initial respondents ($n = 1290$) reported exposure to oil fire smoke odour. Univariate associations of the demographic and psychological variables, and environmental exposures for respondents with complete data ($n = 945$) showed significant associations for mild to moderate 'multisymptom illness' (OR 2.1, 95% CI 1.5-2.9) and severe 'multisymptom illness' (OR 2.9, 95% CI 2.1-4.1). In the multivariate logistic regression model predicting 'multisymptom illness', a significant association was shown with exposure to oil fire smoke odour (OR 1.6, 95% CI 1.2-2.1). The authors found that the agreement between responses related to reports of chemical and oil smoke odours during Gulf War deployment, with only fair agreement beyond that, which would have been expected by chance (κ values = 0.20). In addition, other analyses of this longitudinal data set suggested that responses to categorical (yes/no) questions about oil fire exposure were not well correlated with modelled total suspended particulate measurements taken by the US Army Centre for Health Promotion and Preventive Medicine personnel who were in the Gulf region during and after the Gulf War. Therefore, this limitation questions the accuracy of the self-reported data. The authors concluded that only six exposures ('oil fire smoke', 'the smell of chemicals in the air', 'having a heater in one's tent', 'using a clinic in the Gulf', 'receiving an anthrax shot', and 'consuming pyridostigmine bromide') of the 12 exposures tested showed a relationship with 'multisymptom illness' after controlling for demographic characteristics and the effect of current psychological distress. The authors concluded that 'Gulf War veteran illnesses' may not be associated with one exposure or Gulf War event but rather with one or more different factors. The Council noted that the limitations of this study as discussed at [126].

129. In a cross-sectional study based on self-reported symptoms by Gray et al⁴⁶ the association between 34 different exposures and 'Gulf War illness' (Gray-defined) was examined. 'Gulf War Illness' was defined as having any one of five conditions: a self-

reported physician diagnosis of chronic fatigue syndrome, post-traumatic stress disorder (PTSD), multiple chemical sensitivity, or inflammatory bowel disease or self-reporting of 12 or more medical problems. Questionnaire data were received from 11 868 US Seabees: 3831 Gulf War Seabees (56% response rate), 4933 Seabees deployed elsewhere (30% response rate), and 3104 non-deployed Seabees (15% response rate). Gulf War Seabee respondents were asked questions regarding their experience with 34 possible exposures during the Gulf War. Thirty-three of the 34 exposures examined were univariately associated with 'Gulf War illness', and 12 remained significantly associated in the multivariate analysis.

130. The Council noted that the sample size used in this study was large, which was a strength of the study, with response rates of approximately 70%. However, the Council felt that these strengths were offset by the methodological issues in this study. There were many weak significant associations found in the univariate analysis in this study, which mostly disappeared in the multivariate analysis. Other weaknesses include a non-standard definition of chronic multisymptom illness (author-defined), as well as the reliance on self-reported exposures and self-reported health effects.

131. In terms of oil well smoke, a significant association between exposure to smoke from oil well fires and meeting the case definition of 'Gulf War illness' among 3831 US Gulf War Seabees was found in the univariate analysis (OR 2.22, 95% CI 1.85-2.66) but was non-significant in the multivariable analysis (OR 1.23, 95% CI 0.91-1.65). The authors concluded that the aggregate stresses of war seem to be a more plausible aetiology of illness.

132. In a cross-sectional survey by Haley and Kurt,²⁹ 249 US Gulf War Naval construction battalion veterans self-reported wartime exposures and present symptoms to identify risk factors of factor analysis-derived 'Gulf War related syndromes'. The authors²⁹ found no significant associations between their factor analysis-derived 'Gulf War syndromes' (syndrome 1: impaired cognition; syndrome 2: confusion-ataxia; and syndrome 3: arthromyoneuropathy – Haley-defined) and several risk factors including exposure to smoke from oil well fires. The Council noted the use of cross-sectional study design, the use of retrospectively self-reported exposures and symptoms potentially introduced recall bias. There were also relatively low response rates and the potential for non-response bias.

133. Studies by Sim et al,¹⁹⁻²¹ Kelsall et al,²³ Cherry et al,⁴⁷ and Lange et al⁵⁵ examined associations between self-reported exposure to smoke from oil well fires and a range of symptoms, including respiratory symptoms, but did not directly assess chronic multisymptom illness. Etzel and Ashley⁵⁶ examined the volatile organic compounds in the blood of military Army personnel in Kuwait city and firefighters, medical and para-medical personnel working at the burning oil wells. The 40 firefighters were thought to be 5-10 metres from the burning oil wells with extensive dermal exposure to oil, reportedly without respiratory protection. The study found firefighters had elevated levels of volatile organic compounds in blood, although, the values were low and less than occupational biological limit values. The Council noted that chronic multisymptom illness was not directly assessed.

Studies of Occupational Exposure

134. A number of researchers have studied occupational exposure experienced by firefighters for an association between the occupation of firefighting and increased risk of overall mortality.⁵⁷⁻⁵⁹ No significant associations were found in any of these studies between the occupation of firefighting and increased mortality. The Council noted that chronic multisymptom illness was not assessed in any of these studies.⁵⁷⁻⁵⁹

Council's Conclusions on Studies Concerning Oil Well Smoke:

Overall Quality of the Available Sound Medical-Scientific Evidence

135. In its review of the SMSE, the Council identified two studies that examined exposure to oil well smoke and chronic multisymptom illness (CDC-defined),^{44, 45} two other studies compared two definitions of 'Gulf War illness' (Kansas-defined and CDC-defined chronic multisymptom illness)⁵² and 'Gulf War unexplained illness' (PEHRC-defined and CDC-defined chronic multisymptom illness),²⁸ and two studies used different definitions of 'Gulf War illness' (Gray-defined)⁴⁶ and (Lucas-defined).⁵³ One study examined the association with burn pit emissions and chronic multisymptom illness (CDC-defined).⁵¹

136. Several papers found statistically significant associations between chronic multisymptom illness and self-reported exposure to smoke from oil well fires (Unwin et al⁴⁴, Lucas et al⁵³), oil fire smoke odour (Wolfe et al⁴⁵), and exposure to open-air burn pits (Powell et al⁵¹). However, these studies all had several methodological flaws, including

the self-reported nature of the data, recall bias and low response rates, as discussed previously.

137. Conversely, other studies have failed to show any significant association between 'Gulf War unexplained illness' and self-reported exposure to oil well fires.^{28, 29, 46, 52} A number of reviews^{6, 11, 43} have been conducted but the conclusions from expert committees have been that there is no association between exposure to smoke from oil wells and chronic multisymptom illness.

138. Others examined exposure to smoke from oil well fires and respiratory disease,^{19-21, 23, 55} post-war morbidity from exposure to oil well fire smoke,^{47, 54} and one study examined the biological uptake of oil-fire associated volatile organic compounds concentrations in whole blood of US military Army personnel and firefighters and medical and para-medical personnel working at the burning oil wells.⁵⁶

139. The Council considered that insights into smoke-related morbidity and mortality may be gained by examining occupational studies of firefighters. Three studies of firefighters were reviewed.⁵⁷⁻⁵⁹ Overall, in assessing a potential causal relationship between chronic multisymptom illness and exposure to oil well fire smoke, it is pertinent to note that the neurological symptoms of chronic multisymptom illness have not been associated with firefighting.⁵⁷⁻⁵⁹ Oil well fire smoke constituents are complex, and it was difficult to identify the role of individual substances. The available quantitative Gulf War data and lack of evidence for chronic multisymptom illness in the civilian firefighter literature suggested that oil well smoke was not a risk factor for chronic multisymptom illness.

Summary

140. There was some epidemiological evidence of a significant association between chronic multisymptom illness symptoms and self-reported smoke exposure in Gulf War veterans. Importantly, the quantitative exposure data suggested low-level exposures and low health risk, as judged by environmental health professionals during the oil well fire period.

141. While a significant association was suggested in some studies between exposure to oil well smoke and the development of symptoms of chronic multisymptom illness, the conclusions were not supported by other studies and many of the studies are of limited quality.

THE COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE FACTOR(S) FOR OIL WELL SMOKE

142. In summary, based on the criteria described above at [34-37], the Council considered that the SMSE was insufficient to point to a link between chronic multisymptom illness and exposure to oil well smoke. On that basis, the SMSE does not indicate a reasonable hypothesis connecting chronic multisymptom illness to exposure to oil well smoke. As the Council has concluded that the reasonable hypothesis test was not established, the balance of probabilities test necessarily could not be met.

MEDICAL COUNTERMEASURES - PYRIDOSTIGMINE BROMIDE

Applicant's Contention concerning Pyridostigmine Bromide

143. The Applicant contended that pyridostigmine bromide was given to otherwise healthy individuals, "...approximately one third of whom, two decades following the conflict, are suffering from a debilitating chronic illness, and that it can have serious side effects and interactions when taken in combination with other drugs, vaccines, chemical exposures, heat and/or physical exercise."

144. The Applicant cited Unwin et al^{44(p175, Table9)} who contended that pyridostigmine bromide use was associated with the development of chronic multisymptom illness.

145. The Applicant contended Spencer et al²⁸ reported that taking up to 21 pyridostigmine bromide tablets was associated with an increased risk of chronic multisymptom illness and 'Gulf War illness' in those taking 21 or more pyridostigmine bromide tablets, the risk increased significantly.

146. The Applicant cited Wolfe et al⁴⁵ who found that taking up to 21 pyridostigmine bromide tablets gave a risk of mild to moderate and severe chronic multisymptom illness. The risk of developing mild to moderate, and severe, chronic multisymptom illness symptoms was increased when taking over 21 pyridostigmine bromide tablets.

147. The Applicant cited Gray et al^{46(p1040-41, Table7)} who the Applicant contended found, "taking any dose of pyridostigmine bromide was associated with a risk of developing (study defined) Gulf War illness."

148. The Applicant cited Schumm et al⁶⁰ who reported in a study of 650 US Gulf War veterans found statistically significant rates or signs of ‘Gulf War illness’ (Kansas-defined) relating to the amount of pyridostigmine bromide taken.

149. The Applicant cited Kelsall et al²⁴ in the Australian Gulf War study of 1456 Gulf War veterans, that taking any dose of pyridostigmine bromide was associated with risk in the number of ‘neurological symptoms’ reported.

150. The Applicant contended Haley et al⁶¹ found that a, “...history of advanced acute toxicity after taking pyridostigmine that was correlated with low PON1 type Q arylesterase activity.”

151. In her testimony to the RMA, Professor Beatrice Golomb cited her paper⁶² and stated “For pyridostigmine bromide pills, which had to be taken 3 times a day, people will have had a sense of whether they took one pill, pills for one day (3), for 2 weeks, or for 2 months – and dose-response data repeatedly showed powerful relations to health.”

The Council’s Assessment of the Sound Medical-Scientific Evidence Concerning Pyridostigmine Bromide:

Background

152. Pyridostigmine bromide is a reversible binder of acetylcholinesterase,⁸ and has been used for many decades in the treatment of myasthenia gravis, an autoimmune neuromuscular disorder.¹⁹⁻²¹ Pyridostigmine bromide promotes an increase in levels of acetylcholine at the neuromuscular junction to reduce symptoms of weakness. Adverse reactions, which generally occur at high doses due to the increase in acetylcholine include muscarinic reactions (nausea, vomiting, diarrhoea, abdominal cramps, miosis and increased peristalsis, salivation, bronchial secretions, and heavy perspiration) and nicotinic effects (muscle cramps, fasciculations and weakness).¹⁹⁻²¹ In consideration of the long-term effects of pyridostigmine bromide, the IOM reported that in 2009 the US Food and Drug Administration summarised the existing knowledge of the pyridostigmine

⁸ Acetylcholinesterase is the enzyme that is responsible for the breakdown of acetylcholine and therefore the termination of its activity. Acetylcholine is a neurotransmitter that acts at two major receptor subtypes, nicotinic and muscarinic. There are several neurotransmitters in the body, with acetylcholine being one of the most common. Neurons that use acetylcholine as a neurotransmitter are referred to as cholinergic. Binding of acetylcholine to receptors at neuromuscular synapses leads to the activation of muscles.¹³²

bromide and concluded “that despite a long history of PB being used in the treatment of myasthenia gravis no evidence of long-term health effects has emerged to date.”^{11(p268)} Others have made similar observations.^{4, 63}

153. During the 1990-1991 Gulf War, pyridostigmine bromide was used as an investigational agent as a pre-treatment adjunct to protect military personnel from the toxic effects of a particular nerve agent soman and related nerve agents. Pyridostigmine bromide blocks the action of soman on acetylcholinesterase. Doses recommended for military personnel were 30 mg, given every eight hours prophylactically⁹ if there was a reasonable possibility of a chemical weapons attack, and taken as long as the threat was credible.^{19-21, 64, 65} Much higher doses of pyridostigmine bromide are used to treat certain medical conditions see [185].

154. Accordingly, the use of pyridostigmine bromide varied between individuals, ships, and units depending on the perceived risk of exposure and self-compliance with medication.²⁴ In a study of the acute side effects of pyridostigmine bromide, about half the veteran population who were administered the drug experienced side effects such as increased flatus, abdominal cramps, soft stools, and urinary urgency, with 1% having side effects that warranted medical attention, but fewer than 0.1% had effects sufficient to discontinue the drug.⁶⁵

Reports, Reviews and Meta-analyses

155. Of the available reports, reviews, and meta-analyses the Council considered the best evidence on exposure to pyridostigmine bromide was documented in several IOM reports.^{4, 7, 11} The Council also paid particular attention to a RAC report by Binns et al,¹ a RAND review by Golomb⁶⁴ and reviews by Golomb⁶² and Greenberg and Wessely.⁶⁶

156. In the 2000 IOM Volume 1: Depleted Uranium, Sarin, Pyridostigmine Bromide, Vaccines report by Fulco et al,⁴ the IOM committee concluded that there was sufficient evidence of an association between pyridostigmine bromide and transient acute cholinergic effects in doses normally used for treatment and for diagnostic purposes. The IOM committee concluded that there was inadequate/insufficient evidence to determine

⁹ Doses of pyridostigmine bromide used in the Gulf War were modest compared to those doses used in managing patients with myasthenia gravis (30mg three times daily, compared to 180 to 600mg a day respectively).¹⁹

whether an association exists between pyridostigmine bromide and long-term adverse health effects. The IOM committee also noted:

...the evidence that some types of chronic neuropsychological changes may be linked to acute responses to administration of PB, also suggested by Haley and Kurt (1997),²⁹ 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.^{4(p252)}

157. In the 2006 IOM Volume 4: Health Effects of Serving in the Gulf War report⁷ the IOM committee stated that the studies that used self-reported information indicated that there was a higher prevalence of reporting multiple biological and chemical exposures by veterans compared to their non-deployed counterparts. Studies of pyridostigmine bromide generally show a high prevalence of under consumption, and for a smaller subset, over consumption relative to recommended dosages. The IOM committee concluded that, although Gulf War veterans reported higher levels of symptoms that might be associated with exposures in the field, no associations with any specific exposures could be identified.⁷

158. In the 2010 IOM Volume 8: Update of Health Effects of Serving in the Gulf War report,¹¹ the IOM committee concluded that based on a comprehensive review of the human epidemiologic literature, there was sufficient evidence of an association between deployment to the Gulf War and multisymptom illness. However, the IOM committee noted in relation to the RAC report by Binns et al¹ that:

Although the Update committee did not assess the biological plausibility of the link between PB and pesticides and Gulf War illness, in keeping with its charge to examine the strength of association between deployment to the Gulf War and various human health outcomes, the committee critically examined the human exposure studies cited by the RAC as evidence that PB and pesticides are causally associated with Gulf War illness. ...However, in contrast to the RAC report the Update committee found that human epidemiologic evidence was not sufficient to establish a causative relationship between any specific drug, toxin, plume, or other agent, either

alone or in combination, and Gulf War illness. Given this important issue, the Update committee also undertook an assessment of the key experimental research studies that were cited in the RAC report as supporting the plausibility of this association. This focused assessment of the experimental literature, did not meet, in the committee's opinion, a threshold that would lead to the conclusion that any Gulf War illness related problems could reasonably be expected to result from these putative exposures.^{11(p259)}

159. In a RAC report by Binns et al¹ (discussed at [50-54]) the authors found that the evidence strongly and consistently indicated that two Gulf War neurotoxic exposures were causally associated with 'Gulf War illness' and the use of pyridostigmine bromide pills, given to protect troops from effects of nerve agents. The report made the claim that relevant evidence included the consistent association of 'Gulf War Illness' with pyridostigmine bromide across studies of Gulf War veterans, identified dose-response effects, and research findings in other populations and in animal models.

160. In a RAND review by Golomb⁶⁴ it was reported that larger doses of pyridostigmine bromide used for many years in patient with myasthenia gravis do not produce the chronic symptoms seen in Gulf War veterans. The authors stated that this dichotomy is explained by the fact that pyridostigmine bromide produces a normalisation of nicotinic cholinergic function in muscles of patients with myasthenia, in contrast to a raised acetylcholine function in those without myasthenia gravis.⁶⁴ The mechanism of pyridostigmine bromide producing neurocognitive effects has been debated, as it has generally been considered that the drug does not cross the blood-brain barrier, though this has been challenged with the hypothesis that the blood-brain barrier may be compromised by stress.⁶⁴ The author concluded that pyridostigmine bromide cannot be ruled out as a possible contributor to the development of unexplained or undiagnosed illness in some Gulf War veterans.

161. A review by Golomb⁶² stated that increasing evidence suggested excess illness in Gulf War veterans can be explained in part by exposure to organophosphate and carbamate acetylcholinesterase inhibitors, including pyridostigmine bromide, pesticides, and nerve agents. The author referred to papers in the review, which included both the CDC definition and the Kansas definition of chronic multisymptom illness. The author stated that several epidemiological studies reported a link between acetylcholinesterase

inhibitors exposure and chronic symptoms in Gulf War veterans. The author noted that the studies reviewed found a dose-response relationship for pyridostigmine bromide pill number and non-specific symptoms. The author concluded that these findings do not imply that all illness seen in Gulf War veterans was the result of acetylcholinesterase inhibitors, but suggested that acetylcholinesterase inhibitors exposure may account for some of the excess illness seen in Gulf War veterans.

162. In support of the safety of pyridostigmine bromide, the limitations of positive studies and lack of consistent dose-response effect in exposed veterans has been commented on previously.⁶⁶ Greenberg and Wessely⁶⁶ in their review discussed the findings of a Canadian study⁶⁷ where pyridostigmine bromide tablets were used as a prophylactic against possible effects of exposure to some chemical weapons. However, of the three ships sent to the Gulf by the Canadian military, only two used pyridostigmine bromide prophylaxis, yet the rate of illness was the same in personnel from all three ships. Greenberg and Wessely⁶⁶ also stated that many researchers have argued for some years that the combined effect of exposure to acetylcholinesterase inhibitors such as nerve agents, pyridostigmine bromide, and pesticides, are directly causal. However, the Council considered that a long series of authoritative and extensive reviews, produced by number of departments and institutes such as the IOM have been inconclusive.

Randomised Control Trials

163. Roy et al⁶⁸ conducted a double-blind, placebo-controlled crossover trial to determine whether short-term human exposure to pyridostigmine bromide, DEET, and permethrin, at rest or under stress, adversely affects short-term physical or neurocognitive performance. A total of 64 volunteers were exposed to permethrin-impregnated uniforms, DEET containing skin cream, oral pyridostigmine bromide (3 x 30 mg/daily), and corresponding placebos in four separate sessions and the effect on neurocognitive outcome, physical performance, biochemistry and agent concentrations were investigated. The authors concluded that short-term exposure to combined treatment with pyridostigmine, DEET, and permethrin was well tolerated and did not impair physical or neurocognitive performance in the study population.⁶⁸ The study found no physical or neurocognitive effects after pyridostigmine bromide exposure, though the exposure time was very short.

Cohort and Case-control Studies

164. The Council reviewed studies by Spencer et al,²⁸ Steele et al,⁵² and Lucas et al,⁵³ which specifically examined chronic multisymptom illness or 'Gulf War illness' symptoms.

165. In a study by Spencer et al²⁸ discussed at [8281] found with single exposures, an apparent interaction of stress and pyridostigmine bromide was shown and the likelihood of having 'unexplained illness'. In addition, the authors were unable to observe any interaction between the reported use of insecticide and pyridostigmine bromide and the likelihood of unexplained health symptoms. A strength of this study was the clinical evaluation of a large population-based sample of veterans ($n = 443$) to confirm the persistence of specific health symptoms and to rule out explainable diagnoses. A dose-response relationship was explored in this study. The odds ratios for the relationship with PEHRC-defined 'multisymptom illness' were higher for subjects who reported taking more than 21 pyridostigmine bromide pills compared with those who took less. The odds ratio was OR 2.21, 95% CI 1.30-3.75 for 0-21 pills and 3.84, 95% CI 2.00-7.38 for >21 pills. For CDC-defined multisymptom illness the corresponding ORs were 3.15, 95% CI 1.70-5.83 and OR 4.44, 95% CI 2.10-9.38). In the multivariate model, the confidence intervals overlapped considerably, and the associations were not significant.²⁸ The authors concluded that 'Gulf War unexplained illness' was more likely to be associated with combat conditions rather than exposure to substances such pyridostigmine bromide. The authors stated that it was unlikely that the many thousands of veterans with unexplained symptoms are suffering from neurotoxic effects of chemical exposure. The PEHRC case definition was different to the CDC and the chronic multisymptom illness SoP definitions, in that only one of three symptoms from the categories: fatigue, cognitive/psychological or musculoskeletal was required.

166. In a case-control study of self-reported symptoms and exposures by Steele et al⁵² discussed at [116] the results implicated Gulf War exposures, most prominently the use of pesticides and pyridostigmine bromide pills, as significant risk factors for 'Gulf War illness' (Kansas-defined). In the multivariate analysis, a significant association between taking pyridostigmine bromide pills and 'Gulf War illness', by location in theatre was found for 'all veterans' (Adj. OR 2.88, 95% CI 1.68-4.94) and 'veterans in Iraq and/or Kuwait' (Adj. OR 3.50, 95% CI 1.65-7.41) but not for 'veterans not in Iraq or Kuwait'. The authors concluded that a major finding of the study was the prominence of

pyridostigmine bromide and pesticides as risk factors for 'Gulf War illness'. However, the Council noted the significant limitations of this study at [116].

167. In a case-control study of self-reported symptoms and exposures by Lucas et al⁵³ discussed at [120], pyridostigmine bromide was the only continuous exposure significantly associated with 'Gulf War illness' (Lucas-defined). The odds of having 'Gulf War illness' was 1.013 (95% CI 1.00-1.02), and the authors reported an increase in odds of 1.3% for every pyridostigmine bromide pill taken. There were significant trends toward worse health with greater intake of pyridostigmine bromide. The only continuous exposure significantly associated with 'Gulf War illness' was total pyridostigmine bromide intake. The Council noted the study's methodological flaws discussed at [120].

168. In studies by Haley et al⁶¹ and Liu et al⁶⁹ that examined the same subjects using different imaging techniques, the cholinergic effects of physostigmine, on cerebral blood flow was investigated. Haley et al⁶¹ described an experiment that measured brain blood flow with single photon emission computed tomography (SPECT) before and after both ill Gulf War veterans who met the 'Gulf War illness' (Haley-defined) and healthy controls were given physostigmine (short-acting cholinesterase-inhibiting drug). They studied 21 chronically ill Gulf War veterans, 5 with 'Haley-defined symptom complex 1 (Impaired cognition)', 11 with 'symptom complex 2 (confusion- ataxia)', 5 with 'symptom complex 3 (arthro-myoneuropathy)' and 17 age-, sex- and education-matched controls. Liu et al⁶⁹ used the same group of subjects that were studied in the original SPECT study but used a different cerebral blood flow technique to confirm the findings from the SPECT study by Haley et al⁶¹ and to establish a cost effective technique that did not require the use of radiotracers that could be routinely performed on clinical magnetic resonance imaging (MRI) systems. The authors claimed that an abnormal cholinergic response in deep brain structures could be used to explain the chronic encephalopathic symptoms in one of three diagnostic groups of Gulf War veterans with neurocognitive symptoms, based on factor analysis.^{61, 69} The Council noted several methodological issues with this study. Group differences and subject numbers were small, requiring validation in a larger study with appropriate controls, and the diagnostic factor analysis used by this group also had not been validated by other investigators. The Council further noted the authors' conclusion that their findings suggested a potential mechanism rather than provided

evidence of cause. It is therefore difficult to draw any definite conclusion from what can only be classed as a preliminary study.

169. Haley et al⁷⁰ conducted a case-control study to test for an association between neurological illness in Gulf War veterans and characteristics of paraoxonase 1 (PON1). The study included blood samples from 45 subjects studied in an earlier Haley et al⁷¹ study. The 25 ill veterans included 5 with 'Haley-defined symptom complex 1 (Impaired cognition)', 12 with 'symptom complex 2 (confusion- ataxia)', 5 with 'symptom complex 3 (arthro-myoneuropathy)', and 1 each with 'symptom complexes 4-6 (phobia-apraxia; fever-adenopathy, and weakness-incontience)'. The 20 well controls included 10 well battalion members who served in the Gulf War (deployed controls) and 10 well battalion members who had remained in the US during the war (non-deployed controls). The authors found that ill veterans with the six Haley-defined neurologic symptom complexes, defined by factor analysis, were more likely to have a disadvantageous genetic PON1 polymorphism that theoretically makes handling of organophosphate exposure more difficult. The authors concluded that their findings supported their argument that neurological symptoms in some Gulf War veterans were caused by environmental chemical exposures, made more likely by deficient PON1 activity. However, the Council noted there were major limitations in this study. These included low subject numbers. The authors stated that the study was only able to raise "a promising hypothesis" for further exploration. Importantly for the purpose of this review, the Haley case definition is not equivalent to the chronic multisymptom illness SoPs. As such, it was very difficult to correlate the findings of this study with the chronic multisymptom illness SoPs.

170. Other studies do not support the association of genetic susceptibility to toxin exposure in ill Gulf War veterans.^{72,73} Concato et al⁷² conducted a cross-sectional and retrospective longitudinal study to examine relationships of deployment to the Gulf, as well as symptoms after military service, with post-deployment activity of acetylcholinesterase and related enzymes. The study included 488 veterans. Demographic, military, and clinical characteristics were obtained from a population-based cohort study (in 1995 - 1996) and from a nested case-control study (in 1999 - 2002). Stored serum samples were analysed for activity of acetylcholinesterase and related enzymes. Stress (anxiety) or mood disorders, and symptoms compatible with 'Gulf War veterans' illness' (CDC-defined

chronic multisymptom illness) were examined for associations with enzyme activity. The Concato et al⁷² study had larger numbers of subjects (171 with 'Gulf War illness' – CDC-defined chronic multisymptom illness and 176 controls) and found no difference in acetylcholinesterase, butyrylcholinesterase, PON1 or arylesterase activity between the groups. The Council considered this study as having several strengths, including its objectively-derived data and the relatively large participant numbers involved.

171. The study by Hotopf et al⁷³ also used large numbers of subjects. The authors stated they suspected that those who served in the Gulf were exposed to a specific hazard such as pyridostigmine bromide or pesticides that led to a long-term decrease in PON1 activity. The authors found that PON1 activity was lower in veterans deployed to the Gulf, compared with two other large groups of Bosnian peacekeeping forces and non-deployed UK armed forces. There was no difference in activity between symptomatic and asymptomatic Gulf veterans.

172. In a neuropsychological study of Gulf War veterans by White et al⁷⁴, the relationship of central nervous system (CNS) dysfunction on neuropsychological tests to specific chemical exposures experienced in the Gulf was explored. This study was part of a larger project (conducted between 1994 - 1996) that studied outcomes in Gulf War veterans approximately four years after their return from the Gulf War. Three cohorts (Gulf War veterans Devens = 220; New Orleans = 73 and Germany deployed veterans $n = 50$). Only 240 (Devens = 142; New Orleans = 51; Germany = 47) completed the in-person neuropsychological testing and psychiatric diagnostic interviews. Self-reported exposures were related to neuropsychological test performance controlling for PTSD, major depression, and other known covariates of neuropsychological test performance. The authors concluded that Gulf War-deployed veterans performed worse than the Germany-deployed veterans on several specific neuropsychological tests, but, after adjustment for multiple comparisons, only the differences in mood complaints remained significant. The authors also reported no significant association between self-reported exposure to pyridostigmine bromide and neuropsychological test performance.

Cross-sectional Studies

173. The Council reviewed studies by Wolfe et al,⁴⁵ Gray et al,⁴⁶ and Unwin et al⁴⁴ which specifically examined chronic multisymptom illness or 'Gulf War illness' symptoms.

174. In a cross-sectional study by Wolfe et al⁴⁵ discussed at [126], self-reported exposure to pyridostigmine bromide was significantly associated with 'multisymptom illness' in the multivariate logistic regression (step 2). In addition, compared to those who took no pyridostigmine bromide pills, there was an increased risk in those who reported taking 1-21 pills (OR 1.4, 95% CI 1.0-1.9) and >21 pills (OR 2.1, 95% CI 1.4-3.1). Female gender, lower education level, general psychological distress, and six environmental exposures comprised the model with general psychological distress most strongly associated. The Council noted the methodological issues with this study in its discussion at [126].

175. In a study by Gray et al⁴⁶ discussed at [129] of 3831 US Navy Seabees found a significant association between self-reported 'taking any dose of pyridostigmine bromide' and the risk of developing 'Gulf War illness' (Gray-defined) although the magnitude of this association was not strong (Adj. OR 1.43, 95% CI 1.06-1.93). The definition used was less strict than the chronic multisymptom illness definition in the SoPs. The Council found that this study had several methodological limitations, including self-reporting, recall bias (even though photographs of various medications were included in the questionnaire to reduce the potential for recall bias) and the potential confounding influence of news stories. The authors concluded that pyridostigmine bromide and the other significant exposure associations appeared to be too weak and disparate to support a cohesive explanation of post-war morbidity.⁴⁶

176. In a UK study by Unwin et al⁴⁴ discussed at [123] of three military cohorts showed chronic multisymptom illness (CDC-defined) was significantly associated with self-reported exposure to pyridostigmine bromide in all three cohorts (Gulf War: Adj. OR 2.6, 95% CI 2.2-3.1; Bosnia: Adj. OR 3.4, 95% CI 1.7-6.8; and non-deployed Era: Adj. OR 1.9, 95% CI 1.4-2.8).⁴⁴ The authors noted that service in the Gulf War was associated with various health problems over and above those associated with deployment to an unfamiliar hostile environment. The authors concluded that associations of ill health with adverse events and exposures were found in all cohorts, however, they considered that they might not be unique and causally implicated in Gulf War-related illness.⁴⁴ The Council noted the methodological issues with this study in its discussion at [126].

177. A dose-response relationship has been explored by some researchers, and two studies found a small association.^{19-21, 24} In a cross-sectional Australian study by Sim et al¹⁹⁻²¹ discussed at [55], the total number of self-reported general health symptoms in the

month prior, including neuropathic symptoms was associated with several self-reported exposures including pyridostigmine bromide. The authors concluded that a weak dose response relationship was found for taking any dose of pyridostigmine bromide (95% CI 1.2-1.5; $p < 0.001$) and 1–80 tablets (95% CI 1.1-1.5), 81–180 tablets (95% CI 1.2–1.6) and >180 tablets (95% CI 1.2-1.7) with a dose response per categorical increase in number of pyridostigmine bromide tablets taken in those who had taken seen in those who had taken at least one pyridostigmine bromide tablet (95% CI 1.1-1.2; $p < 0.001$). The authors concluded that a weak dose response relationship was found for taking pyridostigmine bromide tablets. The Council noted the relevance of these findings to the chronic multisymptom illness diagnostic criteria was uncertain.

178. In an Australian study by Kelsall et al,²⁴ 1424 male Australian Gulf War veterans were compared with a randomly sampled military comparison group ($n = 1548$). A postal self-reported questionnaire was used to assess the presence of current neurological type symptoms, medically diagnosed neurological conditions, and medical and chemical exposures. A neurological examination was performed as part of a physical assessment. The authors found taking any dose of pyridostigmine bromide was significantly associated with an increase in the mean number of self-reported neurological symptoms by Gulf War veterans (95% CI 1.2-1.8); 1–80 tablets (95% CI 1.0-1.8); 81–180 tablets (95% CI 1.2-2.1); >180 tablets (95% CI 1.2-2.1); and dose-response per category increase in number of tablets taken 95% CI 1.07-1.29). The reporting of neurological type symptoms was associated with increasing numbers of pyridostigmine bromide tablets taken, and with taking anti-biological warfare tablets and using solvents, pesticides, and insect repellents. The authors reported that the lack of any association between pyridostigmine bromide and the Neuropathy Score, (defined solely on the basis of neurological signs, and medical and chemical exposures), suggested that other factors such as information bias, including recall bias, needed to be considered when interpreting these associations.²⁴ The Council noted these limitations and that chronic multisymptom illness criteria were not used in this study.

179. In a study looking at the possible effects of pyridostigmine bromide on long-term health status by Schumm et al⁷⁵ it was shown that only 24% of veterans took their medication according to instruction, whereas 6% took up to twice the recommended dose. Around 16% took less than the recommended dose or none at all. The authors claimed that

pyridostigmine bromide exposure was associated with a decline in self-reported health status, though their data also suggested that other factors were likely to have been involved. The Council noted that chronic multisymptom illness criteria were not used in this study.

180. In a UK study by Reid et al⁷⁶ of three cohorts of British military personnel (Gulf War = 3531; Bosnia = 2050; and non-deployed Era cohort = 2614). The prevalence of multiple chemical sensitivity in the Gulf, Bosnia, and Era cohorts was 1.3%, 0.3%, and 0.2%, respectively. For chronic fatigue syndrome, the prevalence was 2.1% for the Gulf cohort, 0.7% for the Bosnia cohort, and 1.8% for the Era cohort. The study demonstrated a non-significant association between exposure to pyridostigmine bromide and chronic fatigue syndrome (Adj. OR 1.5, 95% CI 0.7-3.4) and multiple chemical sensitivity (Adj. OR 1.6, 95% CI 0.6-4.0).⁷⁶ The authors concluded that the prevalence of chronic fatigue syndrome in Gulf War veteran populations was higher than in civilian population-based studies. However, the prevalence in the Era cohort was also relatively high, and that chronic fatigue syndrome might be associated with military service, or a result of the social class distribution in that population. The Council noted the study did not focus on chronic multisymptom illness but focussed on chronic fatigue and chemical sensitivity. The Council also noted the methodological limitations of using a cross-sectional survey and the potential for self-reporting biases.

Council's Conclusions on Studies Concerning Pyridostigmine Bromide:

Overall Quality of the Available Sound Medical-Scientific Evidence

181. It has been postulated that pyridostigmine bromide exposure may explain some of the chronic symptoms in Gulf War veterans^{1, 62} but the conclusions from expert committees on the role of pyridostigmine bromide have produced conflicting opinions.^{4, 7, 11, 64}

182. Three studies examined the association between exposure to pyridostigmine bromide and the development of chronic multisymptom illness (CDC-defined).^{28, 44, 45} Other studies focussed on 'Gulf War illness' (Gray-defined),⁴⁶ (Lucas-defined),⁵³ (Kansas-defined),⁵² increased number of symptom reporting,¹⁹⁻²¹ increased neurological symptoms,^{24, 70} or neurocognitive symptoms.^{61, 69} A small number of studies showed a weak significant association^{19-21, 24, 44-46, 53, 77} while others found no significant association.^{4, 7, 11, 28}

183. The quality of the available evidence concerning exposure to pyridostigmine bromide and the development of chronic multisymptom illness was limited. The Council noted that of the three papers^{28, 44, 45} which used the CDC definition for chronic multisymptom illness to examine the association between exposure to pyridostigmine bromide, Unwin et al⁴⁴ and Wolfe et al⁴⁵ each found a borderline significant association between pyridostigmine bromide and chronic multisymptom illness. Unwin et al⁴⁴ found significant associations between chronic multisymptom illness and self-reported exposure to pyridostigmine bromide pills for all three cohorts in the study (Gulf War, Bosnia and non-deployed Era cohorts) and suggested that the association was not unique to the Gulf War. Gray et al⁴⁶ found a weak association between taking any dose of pyridostigmine bromide and 'Gulf War illness' that the authors themselves found unconvincing. Steele et al⁵² found a statistically significant association between 'Gulf War illness' and taking pyridostigmine bromide pills by location in theatre for 'all veterans' and 'veterans in Iraq and/or Kuwait' but not for 'veterans not in Iraq or Kuwait'. Lucas et al⁵³ found a significant association between pyridostigmine bromide (the only continuous exposure) and 'Gulf War illness'. However, Spencer et al²⁸ found no significant association between taking pyridostigmine bromide pills and chronic multisymptom illness in their multivariable model.

184. However, there were major limitations with the overall quality of the evidence of these papers. All of the studies relied on self-reporting. The paper by Spencer et al²⁸ which reported no significant association, was the only study which combined self-reporting with objective clinical evaluation (discussed in detail at [82]).

185. In all studies, exposure assessment of pyridostigmine bromide in military personnel were based on individuals' recall of the measures they received or took, frequently under stressful situations, and these have seldom been verified by records. This potential for recall bias also contributed to the difficulty in identifying specific causes of the veterans' health problems. It was unclear whether the actual exposure or the belief in exposure was the most important aetiological factor.

186. The Council also noted that the doses of pyridostigmine bromide used in the Gulf War were modest compared to those doses used in managing patients with myasthenia gravis (30mg three times daily, compared to 180 to 600mg a day respectively).¹⁹ In attempting to explain a possible difference in susceptibility to toxicity between Gulf War veterans

and patients with myasthenia gravis, the Applicants have quoted claims that pyridostigmine bromide produces a normalisation of nicotinic cholinergic function in muscles of patients with myasthenia, in contrast to a raised acetylcholine function in those without myasthenia gravis.⁶⁴ In fact, a raised acetylcholine function is also expected in patients with myasthenia gravis to overcome the reduction in the number of functioning acetylcholine receptors, as evidenced by the occurrence of similar systemic cholinergic side effects in myasthenic patients using pyridostigmine bromide. This theory therefore would not explain the apparent unique CNS effects in Gulf War veterans who used pyridostigmine bromide since there are no known CNS deficits or functional changes in myasthenia gravis, which would be protective against the putative CNS effects of chronic pyridostigmine bromide administration. In the 2000 IOM Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines report by Fulco et al,⁴ the IOM committee made the observation that the widespread use of pyridostigmine bromide to treat myasthenia gravis has not typically been associated with short or long-term adverse health effects.

Summary

187. While a significant association was suggested in some studies between exposure to pyridostigmine bromide and the development of symptoms of chronic multisymptom illness, the studies are limited in quality and quantity. Overall, the evidence was too limited to support the biological plausibility of chronic neurological toxicity to pyridostigmine in human studies.

THE COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE FACTOR(S) FOR PYRIDOSTIGMINE BROMIDE

188. In summary, based on the criteria described above at [34-37], the Council considered that the SMSE was insufficient to point to a link between chronic multisymptom illness and exposure to pyridostigmine bromide. On that basis, the SMSE does not indicate a reasonable hypothesis connecting chronic multisymptom illness to pyridostigmine bromide. As the Council has concluded that the reasonable hypothesis test was not established, the balance of probabilities test necessarily could not be met.

MEDICAL COUNTERMEASURES - VACCINATIONS

Applicant's Contentions concerning Vaccinations

189. The Applicant contended that many studies reported that specific vaccines or combinations of vaccinations are associated with increased symptom reporting.
190. The Applicant cited studies by Unwin et al⁴⁴ and Hotopf et al⁷⁸ which it contended found risks for chronic multisymptom illness associated with exposure to vaccinations for anthrax, plague, pertussis, and any biological warfare vaccines. The Applicant also cited a study by Wolfe et al⁴⁵ which found risks for chronic multisymptom illness associated with the anthrax vaccination.
191. The Applicant contended that a study by Gray et al^{46(p1040-41, Table7)} of 3831 US Navy Seabees using a case definition of 'Gulf War illness' found vaccinations presented as risk factors; meningococcus, botulism, anthrax, plague, immunoglobulin G, and typhoid.
192. The Applicant also cited Goss Gilroy Inc.,⁶⁷ Boyd et al,⁵⁰ Mahan et al,⁷⁹ Kang et al¹⁸ and Schumm et al⁶⁰ in support of its contentions.
193. In her testimony to the RMA, Professor Beatrice Golomb, cited Cherry et al,⁴⁷ Chalder et al,⁸⁰ Hotopf et al⁷⁸ and Kelsall et al²² and contended that "...a high number of vaccines have shown a consistent apparent epidemiological connection to Gulf War illness."

The Council's Assessment of the Sound Medical-Scientific Evidence concerning Vaccinations:

Background

194. Vaccines and, in particular, multiple vaccinations have been reported by some authors as risk factors for the development of chronic ill health in Gulf War veterans. Vaccines given to military personnel for the Gulf War have been among the most prominent, and controversial, suspected causes of ill health reported by Gulf War veterans. Most military personnel who served in the Gulf War received multiple vaccinations in preparation for deployment, and many received additional shots in theatre. Two of the vaccines used during the war were intended to protect troops from serious disease, and possible death, in the event of exposure to biological weapons-anthrax and botulinum toxin-that Iraq was believed to possess.¹ Therefore, "in addition to the standard vaccinations before military deployment, about 150 000 troops received anthrax vaccine and about 8 000 troops received botulinum toxoid vaccine."^{11(p14)} The specific vaccines received by

individual military personnel before and during the Gulf War varied, depending on what vaccinations they had previously received, required boosters, the branch of service, and their military occupation. In some cases, vaccination records were kept, and they provided an objective measure of exposure in addition to self-reported vaccinations by troops.¹¹

Reports, Reviews and Meta-analyses

195. Of the available reports, reviews, and meta-analyses the Council considered the best evidence on exposure to vaccinations was documented in several IOM reports.^{4, 7, 11, 17}

The Council also paid particular attention to a RAC report by Binns et al.¹

196. In the 2000 IOM Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines report by Fulco et al⁴ the IOM committee concluded that there was, “inadequate/insufficient evidence to determine whether an association does or does not exist between anthrax vaccination and long-term adverse health effects.”^{4(p16)}

197. In the 2000 IOM report, an Assessment of the Safety of the Anthrax Vaccine on health effects associated with exposures during the Gulf War¹⁷ the IOM committee concluded that the evidence reviewed was of insufficient quality, consistency, or statistical power to allow a conclusion of an association between vaccines and a health outcome in humans.

198. In the 2006 IOM Volume 4: Health Effects of Serving in the Gulf War report⁷ the difficulties in determining the vaccination status of veterans when relying on self-reporting were discussed. However, this IOM committee was not charged to review the associated health outcomes with specific biologic or chemical agents.

199. In the 2010 IOM Volume 8: Update of Health Effects of Serving in the Gulf War report,¹¹ the IOM committee noted that although the Gulf War was relatively brief, military personnel were potentially exposed to numerous harmful agents simultaneously, this included (among a number of exposures) preventative measures such as vaccines. The IOM committee also stated that:

...military personnel might have been exposed to various agents at various doses for various periods. Many of the exposures are not specific to the Gulf War, but the number and combination of agents to which the veterans might have been exposed make it difficult to determine whether any agent or combination of agents is the cause of many Gulf War veterans' illnesses.^{11(p17)}

200. In a RAC report by Binns et al,¹ (discussed at [50-54]) the RAC committee concluded that there was some evidence to support an association between ‘Gulf War Illness’ and multiple vaccinations, but that the evidence was inconsistent or limited in important ways. The authors concluded that the “Gulf War epidemiologic studies have not identified any individual vaccine, including the anthrax vaccine, to be a prominent risk factor for Gulf War illness.” ^{1(p126)}

Cohort and Case-control Studies

201. The Council reviewed studies by Spencer et al,²⁸ Asa et al,^{81, 82} Phillips et al,⁸³ and Steele et al,⁵² who specifically examined chronic multisymptom illness or ‘Gulf War illness’ symptoms.

202. In a case-control study by Spencer et al²⁸ multiple factors potentially responsible for illness symptoms in Gulf War veterans for ‘multisymptom illness’ (PEHRC-defined and CDC-defined chronic multisymptom illness) were examined as discussed at [82]. The authors stated that due to the significant rates of over-reporting of exposure to anthrax and botulinum toxoid vaccines and the likelihood that a significant portion of troops did not know what type of vaccines they had received, the reported exposure to botulinum toxoid or anthrax vaccines was not included in their risk analyses. The Council noted the study’s methodological flaws discussed at [82].

203. A cohort study by Asa et al⁸¹ involved 144 Gulf War era veterans or military employees (58 in the blinded study), 48 blood donors, 40 systemic lupus erythematosus patients, 34 silicone breast implant recipients, and 30 chronic fatigue syndrome patients examined the possible role of an adjuvant containing squalene in ‘Gulf War illness’. Squalene is a naturally occurring molecule, which has been used as part of an adjuvant to boost the immunogenic effect of vaccines, however not all vaccine lots contain squalene as an adjuvant. The substantial majority (95%) of ill deployed ‘Gulf War syndrome’ (CDC-defined chronic multisymptom illness) patients had antibodies to squalene. All (100%) Gulf War syndrome patients immunised for service in Desert Shield/Desert Storm but not deployed, but had the same signs and symptoms as those who did deploy, had antibodies to squalene. In contrast, none of the well deployed Gulf veteran’s had antibodies to squalene. Neither patients with idiopathic autoimmune disease nor healthy controls had detectable serum antibodies to squalene. This study attempted to establish

a link between squalene as an immune factor and Gulf War veteran illness. However, the authors note that the molecular pathology of Gulf War illness requires further exploration and understanding, as does the potential role of squalene antibodies to illness in veterans.

204. Building on their previous work,⁸¹ Asa et al⁸² conducted a study examining anti-squalene antibody positivity and vaccine type. The authors stated that the production of anti-squalene antibodies in 'Gulf War syndrome' patients was linked to the presence of squalene in certain lots of anthrax vaccine. The Council felt that these studies did not positively establish an immune basis for the unexplained illness, and that the conclusions drawn are of a speculative and theoretical nature.

205. Phillips et al⁸³ examined the relationship between squalene antibodies and chronic symptoms reported by 579 Seabees Navy construction workers, 30.2% were deployed Gulf War veterans, 7.4% were defined as having 'chronic multisymptom illness' (Phillips-defined as unusual fatigue and three or more of a list of 38 symptoms), and 43.5% were positive for squalene antibodies. The authors found no significant association between squalene antibody status and chronic multisymptom illness, and concluded that squalene antibody status has no role in Gulf War unexplained illness. The Council observed that this study was in direct contrast to the work of Asa et al discussed previously, and noted the inconclusive nature of a suggested link between squalene antibodies and unexplained illness.

206. In a case-control study by Steele et al⁵² discussed at [116], found no significant associations between veterans who reported receiving vaccines in theatre and 'Gulf War Illness' when other exposures were taken into account.

207. In a cohort study group by Smith et al⁸⁴ where results of self-reported anthrax vaccine exposure were compared to electronic documentation of vaccination, there were no differences between vaccinated and unvaccinated participants in overall measures of health (using the Medical Outcomes Study 36-Item SF Health Survey for Veterans -SF-36V). Only the subset of participants who self-reported they had received the anthrax vaccination, but had no electronic documentation, had consistently lower measures of health, suggesting reporting bias.⁸⁴ The Council felt that the large sample size in this study was a strength of the study, but the sample used may not be representative of the

military population in general (a point identified by the authors themselves). The Council felt that the self-reported nature of the ill-health reported in those with no vaccination record indicated a potential degree of recall bias. The Council has previously noted this as a methodological issue with studies relying on self-reported data.

208. In a cohort study to determine whether anthrax vaccine resulted in adverse health effects in Canadian Forces members eight months after vaccination, Hunter et al⁸⁵ found no significant increase in adverse health effects, using the International Classification of Diseases 10th revision (ICD-10). The Council noted that this study relied on objective medical records rather than self-reported health data. However, the timeframe of the study was relatively short, which limits the ability to extrapolate the findings of this study more generally.

209. Murphy et al⁸⁶ conducted a cohort study of UK armed forces to assess the relationship between health and self-reported vaccinations received, and health and medical records of vaccinations received. A total of 4882 randomly selected military personnel deployed to Iraq since 2003 and a subset of 378 whose vaccination records were accessed were studied. Military personnel who reported receiving two or more vaccinations on a single day were more likely to report symptoms of fatigue and had multiple physical symptoms. However, once medical records were used in the analysis these associations were no longer significant. The authors concluded that the associations seen with self-reported vaccinations were due to recall bias. The Council has previously noted reliance on self-reported data as a significant methodological limitation.

Cross-sectional Studies

210. The Council reviewed studies by Unwin et al,⁴⁴ Wolfe et al,⁴⁵ Hotopf et al,⁷⁸ Chalder et al,⁸⁰ Steele,⁸⁷ Gray et al,⁴⁶ and Kang et al¹⁸ which specifically examined chronic multisymptom illness or 'Gulf War illness' symptoms.

211. In a cross-sectional survey of three UK military cohorts by Unwin et al⁴⁴ discussed at [123], the authors found a slight increased risk of chronic multisymptom illness (CDC-defined) for all Gulf War veterans and anthrax (OR 1.5, 95% CI 1.3-1.7), plague (OR 1.3, 95% CI 1.1-1.6) and any biological warfare (OR 1.5, 95% CI 1.3-1.7) vaccines, but not for pertussis (OR 1.1, 95% CI 0.9-1.4). For Bosnia veterans no significant associations between reported vaccinations and chronic multisymptom illness was shown for anthrax

vaccine (other vaccines were not calculated) and any biological warfare vaccine. Of note, 940 Gulf War veterans had vaccination records and 2242 had no record and 1127 Bosnia veterans had vaccination records and 1718 had no record. Exposures specific to the Gulf were associated with all outcomes, and the Gulf War cohort vaccination against biological warfare, and multiple routine vaccinations, were associated with chronic multisymptom illness. The association between routine vaccinations and adverse health outcomes was significant only in respondents who had not used their vaccination records. This finding suggested a degree of recall bias, which is one of a number of methodological issues with this study that the Council has previously noted at [123].

212. In a cross-sectional study by Wolfe et al⁴⁵ of 945 US Gulf War veterans (with full data), 577 (61%) were defined as having chronic multisymptom illness (CDC-defined), 286 mild to moderate and 281 severe chronic multisymptom illness (discussed at [126]). In the univariate analysis, a significant association between self-reported anthrax vaccination and risk of mild to moderate (OR 1.5, 95% CI 1.1-2.1) and severe (OR 1.9, 95% CI 1.4-2.6) chronic multisymptom illness was found. In the multivariate logistic regression model ($n = 945$) predicting a significant association was shown between chronic multisymptom illness and the anthrax vaccine (OR 1.5, 95% CI 1.1-2.0).⁴⁵ However, the Council noted the methodological issues with this study in its discussion at [126] making interpretation of this result problematic.

213. A cross-sectional study of UK Gulf War veterans by Hotopf et al⁷⁸ explored the relationship between ill health after the Gulf War and vaccines received before or during the conflict. The response rate for the original survey was 70.4% ($n = 3284$), of these, 28% ($n = 923$) had vaccine records. The data from only those who had vaccine records were used. The risk for chronic multisymptom illness (CDC-defined) (after adjusting for rank, age, service and education) in Gulf War veterans found a non-significant risk associated with pre-deployment vaccinations of anthrax (OR 1.2, 95% CI 0.9-1.6), plague (OR 1.2, 95% CI 0.7-2.1) and pertussis (OR 1.0, 95% CI 0.7-1.7). The risk for the chronic multisymptom illness in Gulf War veterans found a borderline risk significantly associated with post-deployment vaccinations of anthrax (OR 1.4, 95% CI 1.0-1.8), plague (OR 1.2, 95% CI 0.9-1.6) and pertussis (OR 1.4, 95% CI 1.0-1.9). The authors concluded that vaccines received before deployment were not associated with most of the outcome measures in contrast to vaccines received during deployment. Of the 923 veterans

included in the analysis, there was a low percentage of people who had vaccinations records (anthrax: 27.1%; plague: 8.2%; and pertussis: 11.2%). Therefore, a large percent of reported exposures relied on self-reports from servicemen and were prone to recall bias. In a re-analysis of Gulf War vaccinations data, Hotopf⁸⁸ entered the two separate exposures (pre-deployment vaccines and vaccines received during deployment) in the same model and calculated the differences in regression coefficient for each of the outcome measures. This re-analysis found no significant differences. The author concluded that the results of the re-analysis using an alternative method indicated that there may be no difference in the effects of multiple vaccines on health according to whether they were received before or during deployment. The Council considered this to be a well-conducted study since it took into account the recall bias potential of self-reported data, and also made use of objective medical records, which documented exposure.

214. A study was conducted by Chalder et al⁸⁰ in a random sample of British veterans who served in the Gulf War who believed they had 'Gulf War syndrome' (CDC-defined chronic multisymptom illness). Self-report questionnaires were sent out to a random sample of 4250 Gulf war veterans and 2961 responded (response rate 69.7%). Overall, 513 of the 2961 Gulf war veterans (17.3%, 95% CI 15.9%-18.7%) believed they had 'Gulf War syndrome'. Of those who believed they had 'Gulf War syndrome' 462 (90%) met the CDC definition for chronic multisymptom illness. Participants were asked about the number of vaccines they received before and during deployment. In the unadjusted analysis the higher number of vaccines received was associated with the belief of having 'Gulf War syndrome'. In the adjusted analysis, there was no association between the number of exposures and the belief, however, those who had received more than seven vaccinations and knew other people with 'Gulf War syndrome' were more likely to believe they had 'Gulf War syndrome' ($p < 0.05$). The Council felt that there were major limitations to this study, in particular the self-reported nature of the exposures and the self-diagnosis of "Gulf War syndrome."

215. Steele⁸⁷ conducted a population-based cross-sectional survey of 1548 veterans who served in the Gulf War and 482 veterans who served elsewhere (non-Gulf War). The study examined the association between self-reported exposures and 'Gulf War illness' (Kansas-defined and CDC-defined chronic multisymptom illness). 'Gulf War illness' (CDC-

defined) occurred in 47% of Gulf War veterans, 23% of non-Gulf War veterans who reported receiving vaccines during the war, and 15% of non-Gulf War veterans who did not receive vaccines. Among non-Gulf War veterans, 'Gulf War illness' (CDC-defined chronic multisymptom illness and Kansas-defined) was only significantly associated with self-reported receipt of vaccines (Kansas: OR 3.78, 95% CI 1.50-9.54 and CDC: OR 2.04, 95% CI 1.15-3.60). The authors suggested that non-Gulf War veterans who self-reported exposure to vaccines during war service may experience some of the same health problems as Gulf War veterans. The Council noted a number of methodological issues and limitations with this study, also acknowledged by the authors, including the fact that 15% of Gulf War-era veterans whose military records indicated that they had not served in the Gulf War reported that they had, and the possible impacts of differential recall and the degree of media attention to Gulf War-related health problems.

216. A cross-sectional study by Gray et al⁴⁶ discussed at [129] found associations between self-reported symptoms and vaccinations for anthrax, immunoglobulin G, and botulism. Meeting the case definition of 'Gulf War illness' (Gray-defined) among 3831 Gulf War Seabees was univariately significantly associated with receipt of each of the following vaccinations; meningococcal, botulism, anthrax, plague, immune globulin, and typhoid. However, these significant associations were no longer seen in the multivariate model, although receipt of botulism vaccine was of borderline statistical significance (Adj. OR 1.37, 95% CI 1.00-1.88). The Council noted the essentially negative findings of this study, and the limitations of this study as discussed at [129].

217. In a cross-sectional study by Kang et al¹⁸ discussed at [86], exploratory factor analysis was applied to the 47-symptom correlation matrix of 10 423 US Gulf War veterans and 8960 non-Gulf War veteran respondents. Gulf War veterans who had all of the self-reported symptoms consistent with neurological impairment factor (cases = 277 and controls = 6730), reported exposure to the botulism vaccine (26.3% and 9.2% respectively) was significantly different ($p < 0.0001$). The authors also reported the anthrax vaccine was received by 55.8% of the suspected cases and 35.6% of the control veterans, however, no further analysis was reported. The significant limitations of this study have already been discussed at [8586].

218. In the cross-sectional survey component of the AGWVHS by Sim et al¹⁹⁻²¹ discussed at [55] found the number of vaccinations, 10 or more, were associated with higher

symptom reporting. In particular, musculoskeletal, psychological, skin, respiratory and neurological conditions, lower perceived physical health status and greater functional impairment in Gulf War veterans at baseline were shown. The number of vaccinations reported was also associated with PTSD and psychological distress. Approximately 51% of the baseline study found Gulf War veteran participants had their International Certificate of Vaccination to refer to when reporting their vaccinations status, and 48% provided evidence of their certificate. The Council noted that this study did not examine specifically or report on the association between vaccinations and chronic multisymptom illness.

219. In a cross-sectional study by Kelsall et al²² discussed at [88], increased symptom reporting was associated with several exposures, including having more than 10 immunisations. The total number of symptoms was significantly associated with having at least 10 immunisations (OR 1.3, 95% CI 1.1-1.6), but not with having any immunisations or with having a cluster of immunisations. The total number of symptoms was also greater in those who reported that they did not know the number of immunisations they had received (OR 1.1, 95% CI 1.0-1.2). The authors concluded that increased symptom reporting did not appear to be due to over-reporting or participation bias and that there did not appear to be a unique single exposure associated with increased symptom reporting.²²

220. In a later study, Kelsall et al²⁵ conducted a cross-sectional comparison of self-reported and recorded vaccinations and health effects in Australian Gulf War veterans using the same sample as Kelsall et al.²² The associations of increasing number of self-reported vaccinations in dose response relationships with total number of symptoms, functional impairment, and poorer physical health were not observed when based on recorded vaccination data. Although the actual difference in estimates was small and showed a significant association for total number of symptoms. The findings indicated that reliance on self-reported data will usually lead to incomplete yet over-reporting of vaccination data. The authors suggested that recall or reporting bias may explain associations between self-reported vaccinations and adverse health effects, whereby veterans who reported symptoms or adverse health effects were also more likely to recall and report more exposures, such as vaccinations, than veterans who did not report adverse health outcomes. The authors concluded that vaccinations were not associated with adverse

health effects when exposure assessment was based on recorded vaccinations. As noted previously, the Council considered a major strength of both of these studies was the use of recorded vaccination data to provide objective evidence of actual exposure.

221. In a cross-sectional study, Mahan et al⁷⁹ evaluated the health status of US Gulf War veterans who reported receiving the anthrax vaccination. Among the 11,441 Gulf War veterans who completed the health survey, 4601 reported receiving the anthrax vaccine during the war; 2979 veterans reported not receiving it; 3861 were uncertain if they received it or not. Also, 352 of these respondents were documented by the Department of Defense as having received anthrax. The authors found statistically significant differences in prevalence for health outcomes between those who reported having anthrax vaccination and those who did not. However, once vaccination records were used in the analysis these differences were no longer significant. The Council has previously noted the methodological weaknesses of relying on self-reported data, but felt that the use of objective vaccination records was a strength of this study.

222. Goss Gilroy Inc.⁶⁷ reported a cross-sectional study of 3133 Canadian Gulf War veterans and 3439 control subjects (response rate was 73.0% for Gulf War veterans and 60.3% for controls). Gulf War veterans reported higher prevalence of 19 long-term health problems including musculoskeletal problems fatigue, cognitive dysfunction, fibromyalgia, depression and anxiety. In the adjusted prevalence odds ratios, exposure to non-routine vaccinations of anthrax and plague and self-reported symptoms of cognitive dysfunction and chronic fatigue were statistically significant for Gulf War veterans only (OR 1.28, 95% CI 1.08-1.51 and OR 1.92, 95% CI 1.47-2.50, respectively). The authors concluded that Gulf War veterans demonstrated a higher prevalence of most long-term reported health conditions when considered as a single reported condition or symptom, or in combinations of reported symptoms (symptom clusters or combined health outcomes). However, the Council noted that the results must be considered in the context of the methodological limitations of the study such as potential for over-reporting and recall bias.

223. In a cross-sectional study by Cherry et al⁴⁷ examining self-reported exposures documenting 95 symptoms reported in the month prior to the health questionnaire. Symptom and exposure questionnaire responses were completed seven or more years after the war, and 7971 veterans deployed in the Gulf, from two exposed cohorts, were

included. They authors found consistent but weak correlations in the multivariate analyses of a number of exposures. The analyses included the number of inoculations, which was also specifically associated with higher scores on a factor weighting of symptoms associated with “peripheral” (skin and musculoskeletal) complaints. Similar patterns were obtained in those with and without an official record of inoculations. The Council noted it was difficult to correlate these results with chronic multisystem illness.

224. In a cross-sectional study by Boyd et al⁵⁰ the association of multiple exposures, stressors, and life events with various illness symptoms reported by 978 veterans who believed they had ‘Gulf War-related illness’. Of the 2011 mailed questionnaires, 1161 were completed and returned by the respondents (response rate 60.0%) and 978 were included in the study. The two symptom groups (high symptoms and low symptoms) reported receiving the botulism (OR 1.78, $p = 0.02$) and anthrax vaccine (OR 1.72, $p = 0.03$) at rates that were not statistically different. The other prophylactic treatments (including typhoid and plague vaccinations) were also not reported at significantly different rates. The authors did not find a significant association between botulism or anthrax vaccines with high or low symptom group membership. The authors noted the methodological issue of the self-reported nature of the data giving rise to recall bias (which the Council agrees with).

225. Schumm et al⁸⁹ conducted a cross-sectional study of over 900 US Reserve Component Gulf War Era veterans from Ohio and nearby US states. They found that Gulf War veterans were more likely to report poorer health than non-Gulf veterans. Female veterans were more likely to report mild or severe reactions to vaccines than male veterans. The authors found that veterans who received the anthrax vaccine reported more reactions than those who did not receive anthrax vaccine. They also found that declines in long-term subjective health were associated with the anthrax vaccine by Gulf War veterans but not for subjects who were not deployed to the Gulf, although few of the non-deployed subjects received anthrax vaccine. The authors reported that regardless of deployment status, veterans who reported more severe reactions to vaccines were more likely to report declines in subjective health. The Council noted that chronic multisymptom illness criteria were not used in this study.

Council's Conclusions on Studies Concerning Vaccinations

Overall Quality of the Available Sound Medical-Scientific Evidence

226. The quality of the available evidence concerning exposure to vaccinations and the development of chronic multisymptom illness was limited. Six studies examined the association between exposure to vaccinations and the development of chronic multisymptom illness (CDC-defined).^{28, 44, 45, 78, 80, 81} One study defined 'Gulf War Illness' using both the chronic multisymptom illness and the Kansas definition (Kansas-defined and CDC-defined).⁸⁷ Other studies focused on 'Gulf War illness' (Kang-defined),¹⁸ (Gray-defined),⁴⁶ (Kansas-defined),⁵² increased symptom reporting^{19-22, 25, 50, 79} and other reported health problems.^{47, 67, 82, 84, 85, 89} A small number of studies showed weak significant associations^{19-21, 24, 44-46, 53, 77} while others found no significant associations.^{4, 28}

227. The Council noted that of the six papers^{28, 44, 45, 78, 80, 81} that used the CDC definition for chronic multisymptom illness to examine the association between exposures to vaccinations, four demonstrated significant associations.^{44, 45, 80, 81} Unwin et al⁴⁴ reported significant associations between Gulf War veterans with chronic multisymptom illness and receiving anthrax, plague and any biological warfare vaccination. Chalder et al⁸⁰ demonstrated that those who had received more than seven vaccinations were more likely to believe they had chronic multisymptom illness. Wolfe et al⁴⁵ showed a significant association between chronic multisymptom illness and the anthrax vaccine. Asa et al⁸¹ found that the production of anti-squalene antibodies in Gulf War veterans with chronic multisymptom illness was linked to the presence of squalene in certain lots of anthrax vaccine.

228. Two studies^{28, 78} did not find a significant risk associated with the development of chronic multisymptom illness. Spencer et al²⁸ examined multiple risk factors in a case-control study supported by objective clinical evaluation (discussed at [82]). The authors noted that due to the documented significant rates of over-reporting of anthrax and botulinum vaccinations and the likelihood that a significant portion of troops did not know what type of vaccines they had received, they did not assess reported exposure to botulinum toxoid or anthrax vaccines in the risk analyses of their study. Hotopf et al⁷⁸ found no significant risk for chronic multisymptom illness associated with pre-deployment vaccinations of anthrax, plague and pertussis, and a borderline significant risk associated with post-deployment vaccinations of anthrax, plague and pertussis.

However, when corrected for all vaccines simultaneously any associations were no longer seen.

229. In general, there were major limitations with the overall quality of the evidence, particularly the use of self-reported exposures^{18, 45-47, 50, 52, 87, 89} the accuracy of which has been questioned. The Council noted that a small number of studies by Smith et al,⁸⁴ Murphy et al,⁸⁶ Mahan et al⁷⁹ and Hotopf et al⁷⁸ used objective measures of exposure by using the vaccination record card or medical record. The Council considered the findings of these particular studies to be more informative and reliable, given the use of objective medical records.

230. An association between vaccinations and an immune response has been proposed by some authors as an explanation for the ill health reported by Gulf War veterans.^{81, 82, 90, 91} It has also been claimed that squalene, an organic polymer may have been used as an adjuvant in anthrax vaccines, and that the presence of anti-squalene antibodies was correlated with the development of chronic symptoms, suggesting a possible immunological aetiology.¹ This relationship was linked to certain anthrax vaccine lots which contained squalene.⁸² However, in a study employing a large number of subjects, Phillips et al⁸³ found no significant association between squalene antibody status and chronic multisymptom illness.

231. An association between reported severe reactions to anthrax vaccination and subsequent development of declining health has also been suggested⁸⁹ though another study showed no difference in adverse health effects in the eight months after vaccination.⁸⁵ Other surveys of self-reported exposures by Wolfe et al⁴⁵ and Boyd et al⁵⁰ suggested an association between anthrax vaccination and chronic multisymptom illness.

232. Other surveys of self-reported exposures by Boyd et al⁵⁰ and Kang et al¹⁸ suggested a significant association between botulism vaccination and chronic multisymptom illness. However, Gray et al⁴⁶ found no independent significant associations between the development of 'Gulf War illness' and botulism or anthrax vaccination. In other studies vaccinations were associated with increased symptom reporting.^{67, 79}

233. Several studies surveying self-reported symptoms suggested an association of multiple vaccinations with chronic ill health in Gulf War veterans^{22, 44, 47, 78, 80, 88} as well as in other veterans⁸⁷ and one study reported that this effect was strongest for vaccines given during

deployment and not before.⁷⁸ Another study reported that, while receipt of multiple vaccinations was a risk factor for the development of symptoms in Gulf War veterans, it was not an important factor for the development of chronic symptoms.⁹² Some authors have claimed that there was an issue with poor recording of vaccinations in medical records⁸⁹ and the accuracy of the data has been questioned.⁹³ It has also been claimed that the relationship between illness and multiple vaccinations may be affected by recall bias.^{25, 79, 94}

234. Several expert committees reviewed the available literature and have concluded that there was no firm evidence of a significant association between vaccinations and long-term adverse health effects.^{4, 7, 17, 95}

Summary

235. The biological mechanism of any putative relationship between vaccinations and the development of chronic multisymptom illness remains obscure. The studies that have investigated a possible immunological mechanism have produced conflicting results and there do not seem to be any other coherent mechanisms.

236. Although the quality of the available SMSE was limited (largely due to reliance on self-reported data), the Council considered the most informative studies on exposure to vaccinations and the development of chronic ill health in Gulf War veterans were those studies where vaccination books, electronic documentation of vaccinations and medical chart reviews were used to support data analysis.^{25, 44, 78, 84, 85} Of these studies, four found no significant association between vaccinations and the development of chronic ill health in Gulf War veterans,^{25, 44, 84, 85} and the only significant study⁷⁸ produced conflicting results when the data were re-analysed using a different method.⁸⁸

237. Overall, there was insufficient evidence to identify a definite pathophysiological link between objectively documented exposure to vaccines and the development of chronic multisymptom illness.

THE COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE FACTOR(S) FOR VACCINATIONS

238. In summary, based on the criteria described above at [34-37], the Council considered that the SMSE was insufficient to point to a link between chronic multisymptom illness and vaccinations. On that basis, the SMSE does not indicate a reasonable hypothesis

connecting chronic multisymptom illness to vaccinations. As the Council has concluded that the reasonable hypothesis test was not established, the balance of probabilities test necessarily could not be met.

CONTAMINATED FOOD AND WATER

Applicant's Contentions Concerning Contaminated Food and Water

239. The Applicant contended that a study by Unwin et al^{44(p175, Table9)} of 2735 UK Gulf War veterans found an association between the consumption of local food and chronic multisymptom illness.

240. The Applicant cited Haley et al²⁹ who conducted a study on 249 US Navy Seabees, contended that the authors identified risks for impaired cognition, confusion-ataxia illness and arthro-myoneuropathy illness associated with the 'consumption of drinking water that had a petroleum taste'.

241. The Applicant cited Gray et al^{46(p1040-41, Table7)} to support an association between 'Gulf War illness' and contaminated food. The Applicant cited Kang et al¹⁸ to support an association between 'eating food contaminated by oil well smoke or oil', had an associated risk for a "unique" Gulf War neurological symptom complex." The risk of a "unique" Gulf War neurological symptom complex was increased 'in veterans whom bathed in or drank contaminated water'.

242. The Applicant also cited Boyd et al⁵⁰ for increased symptom reporting associated with eating local food and drinking local water.

The Council's Assessment of the Sound Medical-Scientific Evidence Concerning Contaminated Food and Water:

Background

243. Military personnel deployed to the Gulf War were potentially exposed to food and water contaminated with oil, through the consumption of locally sourced food, or drinking, bathing in, or brushing teeth with contaminated water. There were also reports of another potential source of contamination for military personnel located near oil well fires from 'oil rain', with troops in those areas described being completely soaked with oil and having their food and water taste like oil.¹

Reports, Reviews and Meta-analyses

244. Of the available reports, reviews, and meta-analyses the Council considered the best evidence on exposure to contaminated food and water was documented in a report by the IOM⁷ and the Council also closely reviewed a RAC report by Binns et al.¹
245. In the 2006 IOM Volume 4: Health Effects of Serving in the Gulf War report⁷ the IOM committee stated there were many reports of Gulf War deployed veterans reporting gastrointestinal symptoms and that those symptoms were linked to reports of exposures to contaminated water and burning of animal waste in the war theatre.
246. In a RAC report by Binns et al¹ (discussed at [50-54]), the authors concluded that “overall, it appears unlikely that food and water contamination were major causes of Gulf War illness for most ill veterans.”¹ (p211)

Cohort and Case-control Studies

247. The Council reviewed a study by Gray et al⁴⁶ which specifically examined symptoms of ‘Gulf War illness’.
248. A case-control study of Gulf War US Seabees by Gray et al⁴⁶ discussed at [129] found a statistically significant association between self-reports for ‘drinking contaminated water’ and ‘Gulf War illness’ (Gray-defined) (Adj. OR 1.71, 95% CI 1.32-2.23). However, the authors⁴⁶ noted that their work and that of others⁹⁶ has demonstrated that recall bias was a problem among Gulf War veterans, with the potential for veterans to over-report symptoms and exposures. Of the 845 cases of ‘Gulf War illness’, 126 met the case definition solely on the basis of self-reporting 12 or more medical problems. The Council noted the limitations of this study as discussed at [129].
249. In an Australian study by Sim et al¹⁹⁻²¹ discussed at [55] the proportion of Gulf War veterans reporting exposure to ‘eating contaminated or local food’ was similar to Danish, UK or US Gulf War veterans, although Australian Gulf War veterans reported higher exposures to local waters and drinking water from local taps or wells. Overall, Gulf War veterans were more likely to report a higher number of symptoms and to report symptoms that were more severe. Neuropsychological and musculoskeletal symptoms were amongst the symptoms most commonly reported. However, for Australian Gulf War veterans no significant associations were found between the increased rates of reporting of all symptoms and exposure to contaminated food and water in the Gulf

War.¹⁹⁻²¹ The Council considered these studies to be methodologically strong, as they were a comprehensive examination of health outcomes in veterans coupled with objective health assessments.

Cross-sectional Studies

250. The Council reviewed studies by Unwin et al,⁴⁴ Haley and Kurt,²⁹ and Kang et al¹⁸ which specifically examined chronic multisymptom illness or 'Gulf War illness' symptoms.

251. In a cross-sectional study of UK Gulf War veterans by Unwin et al⁴⁴ discussed at [123], self-reported exposure to 'eating local food' and chronic multisymptom illness (CDC-defined) showed no significant association for the Gulf War cohort (OR 1.1, 95% CI 0.9-1.3) and significant association for the Bosnia cohort (OR 1.8, 95% CI 1.5-2.3). Statistics were not calculated for the non-deployed Era cohort.

252. A survey of US Gulf War Naval construction battalion veterans by Haley and Kurt²⁹ discussed at [132] aimed to identify risk factors for factor analysis-derived 'Gulf War-related syndromes'. In the multivariate analysis no significant association was found between all three 'Gulf War-related syndromes' – Haley-defined (syndrome 1: impaired cognition; syndrome 2: confusion-ataxia, and syndrome 3: arthro-myoneuropathy) and exposure to 'drinking water that had petroleum taste'. The Council did not place much weight on the findings in this study given the significant limitations discussed at [132].

253. In a study by Kang et al¹⁸ discussed at [86], a significant difference was reported for exposure through eating food contaminated with oil, smoke and having bathed in or drank contaminated water (self-reported) in Gulf War veterans with possible 'neurological syndrome' compared to controls.¹⁸ Although no actual statistics were reported such as odds ratios. The Council noted that all symptoms were based on self-report, not on clinical data, and that the authors reported that dose-response relationships were not studied because of the nature of the dataset.

254. In a study by Boyd et al⁵⁰ discussed at [224] the average self-reported exposure to 'eating or drinking local food or water' was higher among those in the high-symptom group than in the low-symptom group. However, exposure through 'eating local food' was not reported at significantly different rates. The Council has previously noted the methodological issues with this study.

255. In an epidemiological cross-sectional investigation by Suadicani et al,⁴⁹ Danish Gulf War veterans reported more 'neuropsychological symptoms' compared with controls. Independent associations were found for several medical complaints including concentration or memory problems and abnormal fatigue not caused by physical activity. Analysis of the association of a clustering of three to five relevant neuropsychological symptoms with numerous psychosocial, physical, chemical and biological exposures related to deployment in the Persian Gulf showed a significant association between self-reported 'neuropsychological symptoms' and 'bathing in or drinking contaminated water (fumes, oil, chemicals)' (Adj. OR 2.9, 95% CI 1.8-4.6).⁴⁹ However, the Council did not put much weight on these findings, since they relied on self-reporting, did not specifically provide objective data on the contamination itself, and the neuropsychological symptoms used in the study did not all specifically relate to symptoms of chronic multisymptom illness (although memory impairment, sleep disturbance and fatigue are included in the chronic multisymptom illness definition).

Council's Conclusions on Studies of Concerning Contaminated Food and Water:

Quality of the Available Sound Medical-Scientific Evidence

256. Only one study examined the association between exposure to contaminated food and or water and the development of chronic multisymptom illness (CDC-defined).⁴⁴ Other studies focussed on 'Gulf War illness' (Haley-defined),²⁹ (Gray-defined),⁴⁶ (Kang-defined – only neurological problems),¹⁸ increased symptom reporting,^{19-21, 50} and increased neuropsychological symptoms.⁴⁹ A small number of studies showed weak significant associations^{18, 46, 49, 50} and others showed no significant associations.^{19-21, 29, 44}

257. The quality of the available evidence concerning exposure to contaminated food and water and the development of chronic multisymptom illness was limited. The Council noted that of the SMSE identified, only one paper by Unwin et al⁴⁴ used the CDC definition for chronic multisymptom illness to examine the association between exposure to contaminated food. Unwin et al⁴⁴ demonstrated no significant associations between eating local food and chronic multisymptom illness.

258. Overall, there were limitations with the quality of the available SMSE. The use of different outcome measures such as increased symptom reporting of 'Gulf War illness', which was defined differently by different authors, made it difficult to assess the

research about the symptoms defined in the SoPs for chronic multisymptom illness. In particular, the studies had methodological limitations in terms of concentrations or cumulative exposures levels, the possibility of confounding (from other exposures), and recall bias from self-reported health symptoms.

Summary

259. There was limited evidence in the literature examined pertaining to possible biological mechanisms of food or water contamination and chronic multisymptom illness. The evidence was so limited that no firm conclusion could be made between exposure to contaminated food and water and the development of symptoms of chronic multisymptom illness.

THE COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE FACTOR(S) FOR CONTAMINATED FOOD AND WATER

260. In summary, based on the criteria described above at [34-37], the Council considered that the SMSE was insufficient to point to a link between chronic multisymptom illness and exposure to contaminated food and water. On that basis, the comprised SMSE does not indicate a reasonable hypothesis connecting chronic multisymptom illness to contaminated food and water. As the Council has concluded that the reasonable hypothesis test was not established, the balance of probabilities test necessarily could not be met.

CHEMICAL AND BIOLOGICAL WEAPONS

The Applicant's Contentions concerning Chemical and Biological Weapons

261. The Applicant contended that there was sufficient evidence for chronic multisymptom illness being associated with toxic environmental exposures.

262. The Applicant included a letter in its submission to the SMRC from Professor Robert Haley: in it, Professor Haley contended that US and Coalition forces, including the Australian contingent, were widely exposed to low-level sarin nerve gas in fallout from the bombing of an Iraqi chemical weapon production and storage facilities.

263. Professor Robert Haley cited his own paper, Haley et al⁷⁰ which he said demonstrated that ill Gulf War veterans who met the Haley case definition of 'Gulf War Illness' had

lower levels of the Q isoenzyme of PON1-Q, the isoenzyme that most protects from damage by chemical nerve agents including sarin. He contended further that ill Gulf War veterans had significantly lower serum PON1-Q activity than well controls.

264. Professor Robert Haley cited an experiment by Haley et al⁶¹ which measured brain blood flow with single photon emission computed tomography (SPECT) in ill Gulf War veterans who met the Haley case definition and well controls, after the administration of physostigmine. The authors hypothesised that, “if the ill veterans suffered permanent damage to central cholinergic receptors from sarin exposure in the war, their brain metabolism, and thus brain blood flow, would react differently to stimulation of those receptors by physostigmine.”

265. Professor Robert Haley cited Tuite and Haley⁹⁷ and stated that “visual confirmation from weather satellite imagery from the third night of the air campaign (18-19 January 1991) of a huge hot-air mass rising over the Muthanna and Falluja 1, 2 and 3 CW production and storage facilities that were bombed that night, and transiting rapidly the 600 km to US and Coalition troop positions, just as the tens of thousands of nerve gas alarms began sounding. From the well-known level of sensitivity of the M8A1 nerve gas alarm, when the alarms sounded this signalled exposure to ambient concentrations of sarin that exceed the level expected by US Environmental Protection Agency to cause long-term effects.”

266. Professor Robert Haley cited Haley and Tuite⁹⁸ who “demonstrated that the risk of Gulf War Illness measured by our case definition increased dramatically with the number of days on which soldiers heard nerve gas alarms in the area where they were living or working.”

267. The Applicant also cited Tuite and Haley⁹⁷ and contended their study “offered new evidence supporting the widespread low-level chemical weapons fallout following allied bombing of Iraqi chemical weapons storage facilities.”

268. The Applicant cited Unwin et al,^{44(p175, Table9)} Spencer et al,²⁸ Wolfe et al,⁴⁵ and Blanchard et al^{99(p70, Table1)} who they contended found evidence for exposure to chemical warfare agents and chronic multisymptom illness.

269. The Applicant cited Haley and Kurt²⁹ and Steele⁸⁷ who they contended found an association between reported exposure to chemical warfare agents and ‘Gulf War

illness'. The Applicant also contended Kang et al¹⁸ found that reported exposure to nerve gas was associated with an increased risk for a Gulf War "unique" neurological symptom complex and Gray et al⁴⁶ found the use of gas masks were associated with 'Gulf War illness'.

270. The Applicant contended Gulf War veterans experienced increased symptom reporting for those with poison gas exposure¹⁰⁰ those who were assessed as within sight or participated in the Khamisiyah chemical weapons demolition¹⁰¹ and veterans being in a chemical weapons area.²²

The Council's Assessment of the Sound Medical-Scientific Evidence Concerning Chemical and Biological Weapons:

Background

271. The Council noted that while biological warfare agents are mentioned in the scope of the review, the Applicant did not direct the Council to any evidence specific to exposure to biological warfare agents (e.g. anthrax). Further, although some of the literature refers to exposure to 'chemical and biological agents', none of the available papers provided evidence of exposure to specific biological warfare agents in connection with chronic multisymptom illness. For this reason, the Council was not able to draw any conclusions relevant to chronic multisymptom illness for specific biological warfare agents, and it has focussed in its discussion on exposure to the chemical agent sarin, which was the concern of the majority of the literature on this topic.

272. The available evidence on chemical warfare agents focussed primarily on exposures experienced during the Gulf War. Several papers^{28, 44, 45, 72, 87, 98, 99, 102} were specific to chronic multisymptom illness. Another group of papers reported on exposures to sarin following terrorist attacks in Japan¹⁰³⁻¹¹⁰ and the Council considered that those papers, where exposure was established, provided the best quality evidence. These papers were not specific to chronic multisymptom illness.

Gulf War Studies

Background

273. Chemical warfare agents including sarin and cyclosarin, were known to exist and were detected in Iraq during the 1990 - 1991 Gulf War.¹⁴ Sarin (GB; o-isopropyl methylphosphonofluoridate) and cyclosarin (GF; cyclohexylmethylphosphonofluoridate)

are highly toxic synthetic organophosphate compounds, which have extreme potency of action on central, peripheral and autonomic neural pathways.¹⁴ Sarin and cyclosarin exert many of their effects by irreversibly binding to and inactivating acetylcholinesterase, the enzyme responsible for metabolising the neurotransmitter acetylcholine. The inactivation of acetylcholinesterase results in an increase in acetylcholine at cholinergic synapses and overstimulation of muscles and nerves.¹⁴

274. The “G” agents, GB and GF, are considered a subset of organophosphorus compounds, and are discussed here, rather than in the pesticides summary (at page 101) because of their greatly enhanced cholinergic toxicity. The other chemical warfare agent reportedly detected during the Gulf War was sulphur mustard,⁹⁷ which is primarily an incapacitating agent, producing skin blisters and eye injuries that are disabling for a time, recovery usually occurs. However, more severe pulmonary, skin, and systemic poisoning can be fatal.¹¹¹

275. During the Gulf War, sarin and cyclosarin were detected at chemical weapons storage sites in Khamisiyah and two storage sites in central Iraq, Muhammadiyat and Al Muthanna (located 400-500 kilometres south of Khamisiyah).¹⁴ A lesser exposure from chemical warfare agents arose in Khamisiyah during a cease-fire period in March 1991, when the US Army carried out demolition operations at a large Iraqi munitions storage complex at Khamisiyah, Iraq.¹¹² No casualties occurred, and it was only much later determined that nerve agents were destroyed and probably released during the demolition.¹¹¹ Two sites in the complex contained rockets loaded with sarin and cyclosarin and “according to the most recent estimates, the total amount released was 371 kilograms of sarin and cyclosarin combined.”^{14(p14)} The destruction of weapons facilities in the Gulf War was accomplished primarily with high-explosive missiles and bombs, which produce instantaneous and extreme blast forces, shock and pressure waves, and heat. Rather than destroying it, high-explosive bombs, which instantaneously propel their plumes upward with extreme shock and pressure waves, disseminated sarin into the atmosphere as vapour or even liquid mixed with other debris.⁹⁷

276. It was reported by the US Department of Defense, that troops in the vicinity of munitions storage complex at Khamisiyah (within a 50-kilometre radius) might have been exposed to low-levels of these agents during its demolition in 1991. US troops performing demolitions were unaware of the presence of nerve agents, and no air

monitoring was conducted at the time of the demolition, and therefore measurements of sarin and cyclosarin exposure levels were not obtained.^{11, 14}

277. At the start of the Gulf War in January 1991, potential exposure to chemical warfare agents was reported for troops at two storage sites in central Iraq, (Muhammadiyah and Al Muthanna), which sustained damage from air attacks.¹¹¹ The IOM committee reported that “munitions containing 2.9 metric tons of sarin–cyclosarin and 1.5 metric tons of mustard gas were damaged at Muhammadiyah, and munitions containing 16.8 metric tons of sarin–cyclosarin were damaged at Al Muthanna.”^{14(p17)} It has been argued by a number of authors^{97, 98} that exposure to cholinergic chemical warfare agents was low-level (insufficient to cause symptoms of miosis or dyspnoea) and via fallout.

278. A number of different chemical sensors and alarms were distributed throughout the Gulf War region to warn of chemical-warfare attacks as described by Tuite and Haley^{97(p171-72, Table2)} Of the chemical sensors and alarms, predominantly the US M8A1 nerve agent alarms were widely deployed throughout US and Coalition troop concentrations to detect cholinesterase-inhibiting chemical nerve agents.⁹⁷ The M8A1 alarm system is designed to detect nerve agents as vapours or aerosols, responding within less than two minutes to G agents in the range of 0.1 to 0.2 mg/m³. The alarms were extremely sensitive and could be triggered by a large number of interfering chemicals (smokes, fuels, insecticides, paint fumes, cologne, some organic solvents, and vehicle exhaust fumes) and thus produce false alarms.¹¹¹ It was also likely the M8A1 chemical alarms were activated by oil well smoke, based on the principle of instrument operation and the dates/times of the alarms and the reported oil well fires (e.g. 16 January 1991 oil well fire at Wahfra).⁹⁷ The chemical alarms sounded frequently during the early conflict period and documented chemical weapons detection activity was most intense on 19 January 1991.⁹⁷ While minimal in-theatre documentation was retained, records from Tuite and Haley⁹⁷ stated “the number of triggered alarms was estimated by US Department of Defense officials at 2-3 soundings per alarm per day for each of the approximately 14 000 alarms deployed during this period.”^{97(p169)} The chemical alarms sounded and troops responded by dressing in protective kit such as Mission-Oriented Protective Posture (MOPP) and taking pyridostigmine bromide as an antidote to potential nerve gas exposure. In addition to the alarms, there were widespread reports of dead sheep, goats, and camels, which troops were “taught” could indicate the use of chemical or biologic

weapons.¹¹ The alarms, reports of dead animals, and rumours that other units had been hit by chemical warfare agents caused the troops to be concerned that they would be or had been exposed to such agents. The sounding of the chemical alarms by themselves was not diagnostic of exposure.¹¹ However, the exact identities and absolute concentrations of agents causing the alarms to activate were often unknown.⁹⁷

279. The potential exposures to sarin and cyclosarin from the Khamisiyah incident have been the subject of specific modelling to determine potential exposures of US troops. According to model estimates, no troops were exposed to doses which would set off chemical alarms and cause visible signs of the acute cholinergic syndrome.¹⁴ There were no medical reports that were consistent with signs and symptoms of acute exposure to sarin, and available information was consistent with the absence of reports of symptoms of an acute cholinergic syndrome by medical personnel or veterans.¹⁴

Reviews, Reports and Meta-analyses

280. Of the available reports, reviews, and meta-analyses the Council considered the best evidence on exposure to chemical and biological weapons was documented in reports by the IOM.^{4, 11, 14} The Council also paid particular attention to a RAND report by Augerson¹¹¹ and reviews by Tuite and Haley⁹⁷ and Brimfield.¹¹³

281. The 2000 IOM Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines report by Fulco et al⁴ assessed the scientific literature regarding potential health effects of chemical and biological agents present in the Gulf War. The IOM committee concluded that there was inadequate/insufficient evidence to determine whether an association exists between exposure to sarin at low doses insufficient to cause acute cholinergic signs and symptoms and subsequent long-term adverse health effects. The IOM committee stated:

...on the basis of positive findings in a study of non-human primates and studies of humans exposed to organophosphate insecticides, it is reasonable to hypothesise that long-term adverse health effects can occur after exposure to low levels of sarin. Studies of industrial workers exposed to low levels of organophosphate insecticides consistently show a higher prevalence of neurological and/or psychiatric symptom reporting. However, there are no well-controlled studies of long-term health effects in humans exposed to sarin at doses that do not produce acute signs and symptoms.^{4(p10)}

282. The 2004 IOM Updated Literature Review of Sarin,¹⁴ an update on previous IOM reports including that by Fulco et al⁴ on outcomes of exposure to sarin and cyclosarin. The update was in light of more recent studies of sarin exposure from terrorist attacks in Japan; possible sarin exposure of veterans at Khamisiyah, Iraq during the Gulf War; and more recent toxicological studies on low-dose exposure to sarin. The IOM¹⁴ committee noted that from model estimates, there were no reports of troops exposed to doses great enough to cause “first noticeable effects”, which would set off chemical alarms and cause visible signs of the acute cholinergic syndrome. There were no medical reports by the US Army Medical Corps at the time of the release that were consistent with signs and symptoms of acute exposure to sarin. The information was consistent with the absence of reports of acute cholinergic symptoms. The IOM committee concluded that there was inadequate or insufficient evidence to determine whether an association exists between exposure to sarin at low doses insufficient to cause acute cholinergic signs and symptoms and subsequent long-term adverse neurological health effects syndrome by medical personnel or veterans.

283. In the 2010 IOM Volume 8: Update of Health Effects of Serving in the Gulf War report,¹¹ the IOM committee noted that:

The time during which nerve gas may have been released from Khamisiyah is uncertain because there were aerial attacks as well as ground detonations of explosives at this site. No reports of acute symptoms among potentially exposed military personnel have been linked to the nerve gas releases from the Khamisiyah demolition. However, very low-level exposure to sarin or cyclosarin may cause symptoms indistinguishable from systemic viral illnesses or mild bacterial illnesses and thus the symptoms might be confused with other illnesses commonly seen in an unhygienic theater of war.^{11(p269)}

284. In a 2000 RAND report, Augerson¹¹¹ reviewed ‘Gulf War illness’ and exposure to chemical and biological warfare agents and formed four broad conclusions. First, a militarily effective dose of any of the agents considered in the review, would have produced symptoms requiring treatment or would have killed the soldiers exposed. The author found that while there might have been some difficulty identifying a specific agent, no symptoms consistent with exposures to large doses of any of the agents were reported, except one person who was apparently exposed to ‘mustard gas residual’.

Second, the author found that low-level exposures to many of the agents could have produced symptoms similar to those caused by irritation from dust and sand, upper respiratory infections, gastroenteritis, asthma, (none of which are factors in the chronic multisymptom illness SoPs) that were simply overlooked or attributed to other sources. The literature reported no clinical symptoms developing years after exposure. Third, the author found that the literature suggested that some interaction might occur between chemical warfare agents and other factors such as stress, pyridostigmine bromide, and anticholinesterase nerve agents. Fourth, the author noted that very little of the literature has examined the long-term effects of exposures to doses below those that would cause acute clinical symptoms. The authors concluded that considerably more research was needed in this area before even preliminary suppositions could be formulated.¹¹¹

285. In 2013, Tuite and Haley⁹⁷ re-examined the possible role of low-level nerve agent exposure from fallout released by the bombing of Iraqi chemical weapons production and storage facilities early in the air campaign. The authors reviewed the currently unclassified evidence, setting out a case for how nerve-agent-containing fallout from bombings, some of which were hundreds of kilometers away, could have reached US and Coalition troop positions without causing casualties in-between. Specifically, the authors contended:

... the evidence addresses how high kinetic and thermal energy explosions at Iraqi chemical research, production and storage sites would have penetrated the stable nocturnal surface layer of the atmosphere, reaching higher level winds that carried a fallout cloud over US and Coalition positions in northern Saudi Arabia during the course of the night, then triggering the many reported alarms and detections.^{97(p163)}

286. While minimal in-theatre documentation was retained, the high number of triggered alarms and the simultaneous detection of traces of multiple chemical agents, including sarin, tabun and sulfur mustard, in the absence of evidence of a coordinated chemical attack by the Iraqis, was best explained by fallout from bombing of the large storage sites containing large quantities of the several chemical agents. Tuite and Haley⁹⁷ stated that it was reasonable to conclude that sarin exposures to concentrations at or above 0.11 mg/m³ were widespread and repetitive. Miosis and dyspnea were not commonly reported among the exposed troops, but other symptoms compatible with mild cholinergic stimulation, such as stomach cramps, urge to urinate or defecate, and

diarrhea, were common during the conflict period. In the absence of miosis and dyspnea, using protective gear when ambient concentrations triggered alarms may have kept the exposure of any single ambient concentration spike to just at or under the Acute Exposure Guideline Levels threshold. The authors stated that “no matter how quickly protective MOPP gear was put on, some cutaneous and respiratory absorption would have occurred.”^{97(p172)} The authors concluded that the intelligence data provided an explanation, as well as direct confirmation, of how repetitive exposure to low-level sarin nerve agent resulted from fallout that transited long-distance from US and Coalition bombing of the Iraqi chemical weapons research, production and storage facilities during the air campaign of the 1991 Persian Gulf War. The authors recommended that epidemiologic studies of chronic post-war illness should be reassessed using veterans' reports of hearing nerve agent alarms as the measure of exposure. In the case of the early bombings (17 January - 23 February 1991), Tuite and Haley⁹⁷ argued that bombing chemical warfare agents storage facilities would not have destroyed all of the sarin, and that a fraction would have been disseminated in plumes directed upwards from the blast. The Council considered that this was a speculative view, which was not corroborated with any supporting reference or data. The Council noted that a paper by Chang¹¹⁴ reported the shortcomings and methodological errors in the Tuite and Haley paper⁹⁷.

287. In a review, Brimfield¹¹³ stated that the most obvious source of toxicity among the group of compounds thought to be responsible for the symptoms of ‘Gulf War syndrome’ was acetylcholinesterase inhibitors. Of the seven compounds identified in the review, chiorpyrifos, sarin, and cyclosarin fell into this category. They included some extremely potent neurotoxins, which could be responsible for producing a surplus of acetylcholine and, as speculated in the literature, creating neurotoxic effects, even at very low-levels.

Cohort and Case-control Studies

288. The Council reviewed studies by Spencer et al,²⁸ Lucas et al,⁵³ Haley and Tuite,⁹⁸ and Haley et al⁷⁰ which specifically examined chronic multisymptom illness or ‘Gulf War illness’ symptoms.

289. Spencer et al²⁸ discussed at [82], analysed self-reported exposures and their association with ‘Gulf War unexplained illness’ (PEHRC-defined and CDC-defined chronic

multisymptom illness) in Gulf War veterans. The Armed Forces Qualifying Test scores (although the authors did not state what this test measured) did not differ between PEHRC cases and controls, but CDC multisymptom cases had significantly lower scores ($p = 0.013$). Because of the high probability that veterans experiencing health symptoms believe exposure is a likely reason for their symptoms, variables such as 'lack of adequate MOPP protection', and 'work in areas where chemical warfare agents were found' were used as surrogates for exposure to chemical warfare agents. No significant association was seen between 'Gulf War unexplained illness' (PEHRC-defined and CDC-defined chronic multisymptom illness) and veterans reporting they had 'worked around chemical warfare agents', 'heard SCUD alarms' and 'saw SCUD detonate'. A statistically significant association was found between veterans with meeting the criteria for 'Gulf War unexplained illness' (PEHRC-defined and CDC-defined chronic multisymptom illness) and self-reported exposure through 'inadequate protection during chemical/SCUD alarms' (PEHRC cases: OR 2.39, 95% CI 1.03-5.56 and CDC cases: OR 3.16, 95% CI 1.28-7.80). The authors stated that the odds ratios were in general larger when using the CDC multisymptom case definition, but the confidence intervals were wider because of the smaller sample size. In the multivariable logistic regression model of risk factors associated with 'unexplained illness', combat-related exposure (cluster 4), which consisted of variables that described self-reported exposures (such as depleted uranium, exposure to artillery smoke or fumes, working in areas where chemical warfare agents were found or stored, and the Keane combat exposure scale) was significantly associated with 'Gulf War illness' (PEHRC cases: OR 1.62, 95% CI 1.26-2.11 and CDC cases: OR 1.76, 95% CI 1.29-2.40). However, working in areas where chemical warfare agents were found or stored was not assessed separately in the multivariate analysis, and the level of exposure to chemical warfare agents was not reported. The authors concluded that these results indicated that most 'unexplained illness' in Gulf War veterans cannot be explained by neurotoxic effects of exposures to chemicals that inhibit cholinesterase activity. The Council noted multiple simultaneous exposures were analysed. The cluster that included depleted uranium and working in areas where chemical warfare agents were found or stored was found to be significantly associated with 'Gulf War Illness'. However, the singular variable relating to chemical warfare agents was not significantly associated. The cluster that contained pyridostigmine bromide use, oil well fires, DEET and permethrin did not enter the model (i.e. did not affect the model when eliminated).

290. In a case-control study by Lucas et al⁵³ discussed at [120] there was a significant association between 'Gulf War illness' (Lucas-defined) and self-reported use of a chemical suit (OR 3.34, 95% CI 1.05-11.73) but no association was found for 'hearing alarms'. The Council has previously discussed the methodological issues in this study, such as the self-reported nature of the data and the lack of specific focus on chronic multisymptom illness.
291. In a case-control study by Haley et al⁷⁰ as discussed at [169], the authors concluded that Gulf War veterans who met the 'Haley case definition of Gulf War illness' had lower levels of the Q isoenzyme of paraoxonase 1 (PON1-Q), the isoenzyme that most protects from damage by chemical nerve agents including sarin. The Council has previously noted the major methodological limitations of this study, including the case definition used, low sample size and the difficulty in correlating the findings of this study with the chronic multisymptom illness SoPs.
292. Haley and Tuite⁹⁸ conducted a population-based survey designed to test competing hypotheses on the impact on chronic 'Gulf War illness' (Factor Haley-defined and CDC-defined chronic multisymptom illness) of nerve agent from early-war bombing versus post-war demolition. The US Military Health Survey performed computer-assisted telephone interviews of a stratified random sample of Gulf War era veterans ($n = 8020$). Early-war exposure was measured by having 'heard nerve agent alarms' whereas post-war exposure was assessed by the computer-generated plume from the Khamisiyah demolition and physical location of the veteran at the time. A total of 91 974 (13.6%) of the population of Gulf War veterans deployed to the Kuwaiti Theater of Operations in early 1991 were defined as having 'Gulf War illness' (Factor Haley-defined) and 282 398 (41.7%) of the deployed military population as having 'Gulf War illness' (CDC-defined chronic multisymptom illness). Almost all (95%) of those classified as positive by the Overall Factor case definition were also classified as positive by the CDC chronic multisymptom illness case definition. Analysis of the population-representative data from the US Military Health Survey estimated that 248 753 (39%) of the deployed US military force deployed to the Kuwaiti Theater of Operations may have been exposed to low-level nerve agent from fall-out during the conflict period (the five week air campaign plus the five day ground war during which chemical detectors were continuously operating) as indicated by having heard chemical weapon alarms. An estimated 69 799

(11% of the deployed force) 'heard an alarm' only once, 147 997 (23%) 'heard alarms' 2-20 times, and 30 957 (5%) 'heard alarms' more than 20 times. An estimated 95 131 (16%) of the deployed personnel, whose locations were known, were located in the computer-modeled plume of putative exposure to low-level nerve agent from demolition of the Khamisiyah ammunition depot after the end of the conflict period when nerve agent alarms were no longer routinely operating. An estimated 78 665 (12%) were located in the Khamisiyah plume on only one day, and 16 466 (2%) on two or three days. In the multivariate analyses, a significant association between 'Gulf War illness' (Haley-defined: OR 4.13, 95% CI 2.51-6.80; CDC-defined: OR 2.60, 95% CI 2.00-3.38) and having been in 'areas where the chemical nerve agent alarms sounded' was demonstrated. However, no significant association was found for those 'located in the Khamisiyah plume' and 'Gulf War illness' for both definitions. There was a dose-related trend for the number of alarms ($P_{\text{trend}} < 0.001$) but not for the number of days in the Khamisiyah plume ($P_{\text{trend}} = 0.17$). The study found a strong dose-response relationship between the number of times nerve agent alarms sounded in the subject's immediate area and the risk of having 'Gulf War illness' as defined by either case definitions. In contrast, the number of days exposed to the computer-generated plume from post-conflict demolition of the Khamisiyah ammunition depot did not have a dose-response association. The authors contended that meteorological data and associations intelligence data supported the hypothesis that soldiers could have been exposed to chemical warfare agents as far away as northern Saudi Arabia because there seemed to be good evidence for the potential for long distance transit (in the right direction) from infrared weather satellite images. The authors postulated that exposure to low-level sarin nerve agent in fallout from bombing early in the air campaign "may have" contributed more to chronic illness than post-war demolition.⁹⁸ However, the Council viewed this as a speculative conclusion not substantiated by their data.

293. Proctor et al¹¹⁵ examined the neuropsychological test performances (as a potential marker of cognitive impairment) of a subset of 1991 Gulf War veterans from the Devens Cohort Study who underwent a comprehensive in-person evaluation between 1994 and 1996, three and half to five years after Gulf War deployment. Exposure levels were based on modelled estimates of the exposure plume and on troop location information at the time of the Khamisiyah event. Based on this location information, a total of 140 Gulf War veterans were included in the study, 23 veterans were postulated to have received high

(exposure range: >0.072-0.144mg min/m³), 47 to have received moderate (exposure range: 0.01296-0.072 mg min/m³), and 70 had low-to-no exposure (exposure range: <0.01296mg min/m³) dose levels to sarin and cyclosarin at Khamisiyah, Iraq. A number of neuropsychological tests were used to assess five cognitive domains. Significant dose-response relationships between possible exposure and less proficient neuropsychological task performances for psycho-motor dexterity and visuospatial abilities (Purdue Pegboard and Block Designs) were present four to five years following exposure. The authors did point out that the hypothesis examined in this study focussed on exposure to sarin and cyclosarin in the area around Khamisiyah, Iraq in March 1991 and specific neurobehavioral effects four to five years after exposure. The authors considered that the strength of the study was that objective tests of neurobehavioral functioning were conducted prior to the public announcement that the munitions detonated at Khamisiyah contained sarin and cyclosarin, thus reducing the potential likelihood of reporting bias. However, the authors stated that the modeled exposure estimates and thus the exposure-level categories may have been subject to misclassification bias but that this bias was likely to be random and thus would tend to reduce the size of any associations. The Council noted the authors' statement that the focus of their study was not on whether exposure to sarin and cyclosarin was associated with illness in Gulf War veterans. Indeed, the rate of chronic multisymptom illness (CDC-defined) was significantly higher in the low-to-no exposed group than the two higher exposed groups. The authors noted that the aetiology of such illness in veterans is yet to be (and may never be) understood, and has multiple potential confounders. The Council noted that this study involved potential exposure to chemical agents, objective testing, and exposure was not based on self-report. Many of the health and neuropsychological effects seen, however, were not consistent with the chronic multisymptom illness SoPs. The higher rate of chronic multisymptom illness in the low- to non-exposed group casts some doubt on any link between exposure to chemical warfare agents and chronic multisymptom illness.

294. White et al⁷⁴ as discussed at [172], found within the Gulf War deployed group, self-reported exposure to chemical warfare agents was significantly associated with poorer performance on cognitive tests involving specific functional domains. The authors concluded that the study suggested that there are subtle impairments in cognitive function as measured by objective tests and in mood state that can be linked to Gulf War

service and to self-reported exposures in the Gulf War theater. The authors stated that these impairments, “raise the possibility” of CNS damage that was linked to specific self-reported exposures such as chemical warfare agents. The Council considered this to be a speculative conclusion.

Cross-sectional Studies

295. The Council reviewed studies by Wolfe et al,⁴⁵ Gray et al,⁴⁶ Blanchard et al,⁹⁹ Unwin et al,⁴⁴ and Steele,⁸⁷ which specifically examined chronic multisymptom illness or ‘Gulf War illness’ symptoms.
296. Wolfe et al⁴⁵ as discussed at [126] reported the multivariate logistic regression model predicting multisymptom illness (CDC-defined), a significant association with exposure to chemical odour (OR 2.4, 95% CI 1.6-3.6). In the logistic regression stratifying for those who exceeded the clinical cut-off for general psychological distress and those who did not, ‘exposure to chemical odours’ was significantly associated with multisymptom illness (OR 3.3, 95% CI 1.9-5.9) for those who were high in general psychological distress (as per the Global Severity Index of the Brief Symptom Inventory). For those who did not meet the criteria for Global Severity Index of the Brief Symptom Inventory, the association with ‘exposure to chemical odour’ was not provided. Also, different predictors were identified as associated with the outcome, depending on group-level factors, such as level of psychological distress. The Council noted the methodological issues with this study in its discussion at [126].
297. In a cross-sectional study based on self-reported symptoms by Gray et al⁴⁶ discussed at [129], no significant associations were found for the ‘use of gas masks’ and symptoms. The authors concluded that 12 Gulf War exposures were borderline significantly associated with illness, but the exposure associations appeared too weak and disparate to support a cohesive explanation of post-war morbidity. Instead, the authors concluded that the aggregate stresses of war seem to be a more plausible aetiology. The Council noted the methodological issues with this study in its discussion at [129].
298. Blanchard et al⁹⁹ conducted a cross-sectional study to determine the prevalence of chronic multisymptom illness (CDC-defined) among deployed and non-deployed veterans 10 years after Gulf War. Of the 1035 deployed and 1116 non-deployed veterans with complete data included in the analysis, 327 (28.9%) deployed group veterans met the

criteria for multisymptom illness (257 mild to moderate and 70 severe) and in the non-deployed group veterans 165 (15.8%) who met the criteria for multisymptom illness (142 mild to moderate and 23 severe). In the univariate analyses, a borderline significant association was shown between reported 'exposure to munitions explosion in Khamisiyah, Iraq' and 1035 deployed veterans (327 with chronic multisymptom illness versus 708 without chronic multisymptom illness (OR 1.60, 95% CI 0.97-2.64). The authors noted that according to Department of Defense modeling, 236 of the 1035 deployed veterans in the sample may have been exposed to the Khamisiyah munitions explosion, of which 92 had chronic multisymptom illness. The authors concluded that chronic multisymptom illness is more prevalent among deployed veterans than among non-deployed veterans some 10 years after the Gulf War, but with a common manifestation in both groups. The results indicated a chronic multisymptom illness prevalence rate of 15% in veterans who were not deployed to the Gulf. The Council noted that while this study involved objective health assessments, the participation rate was relatively low for both target groups and the authors identified some potential for participation bias and recall bias. The borderline univariate significance for exposure to the Khamisiyah munitions explosion was not considered a convincing result given these issues.

299. Steele⁸⁷ conducted a population-based survey discussed at [215], in which participants were asked questions about their military service. Deployed veterans were asked when they arrived and departed from the Persian Gulf area, the countries they were deployed to, the units in which they served, and whether they had been notified by the Department of Defense that they had been in the area potentially affected by the Khamisiyah munitions demolition in Iraq. A total 271 of 1427 reported 'being notified of proximity to Khamisiyah demolition site' of which 42% had 'Gulf War illness' (Kansas-defined), a significant association was seen in the unadjusted analysis (OR 1.47, 95% CI 1.12-1.92), no significant association was seen once adjusted for sex, income, education level, branch of service, rank, location in theater, and time in theater (OR 1.28, 95% CI 0.95-1.73). The authors concluded that observed patterns suggested that excess morbidity among Gulf War veterans was associated with characteristics of their wartime service and not with specific exposures.

300. Unwin et al⁴⁴ conducted a cross-sectional epidemiological postal survey as discussed at [123]. The authors found an association with the belief of exposure to a chemical attack. Self-reported exposure of 'heard chemical alarms sounding' differed substantially between the three cohorts, 70.7% in the Gulf War cohort compared to only 2.7% in the Bosnia cohort and 6.6% in the Era cohort. Significant associations between chronic multisymptom illness (CDC-defined) and self-reported exposure to 'heard chemical alarms sounding' was shown for the Gulf War cohort (OR 2.2, 95% CI 1.9-2.6), Bosnia cohort (OR 2.5, 95% CI 1.4-4.5) and for the Era cohort (OR 2.3, 95% CI 1.7-3.2). Significant associations between chronic multisymptom illness (CDC-defined) and self-reported exposure to 'use of nuclear, biological, chemical (NBC) suits' was shown for the Gulf War cohort (OR 2.7, 95% CI 2.3-3.3), Bosnia cohort (OR 2.7, 95% CI 1.6-4.8) and for the Era cohort (OR 2.3, 95% CI 1.5-3.7). The authors concluded that Gulf and Bosnia veterans differed in their experience of needing to protect themselves against chemical attack, their perception that such attack might be imminent, and the belief that such an attack had taken place. Whether or not such attack occurred was uncertain, although an accidental discharge of chemical agents did take place after the war at Khamisiyah. The authors stated the findings suggested associations of ill health with adverse events and exposures in all cohorts, however, the authors considered they may not be unique and causally implicated in Gulf War-related illness. Furthermore, they concluded that the threat of exposure (independent of actual exposure) may be a risk factor for adverse health outcomes.

301. Concato et al⁷² conducted a cross-sectional and longitudinal (retrospective) study discussed at [170]. The authors concluded that post-deployment (long-term) serum acetylcholinesterase activity did not appear to be strongly associated with deployment to the Persian Gulf or established symptoms of "Gulf War veterans' illness". The Council noted that the use of objectively-derived data were a strength of this study.

302. Chao et al¹¹⁶ examined neurobehavioural and brain imaging data in Gulf War veterans categorised as having being exposed to sarin/cyclosarin due to their presence in Khamisiyah, Iraq, and compared this data with matched controls. They found no difference between the exposed and non-exposed groups in chronic multisymptom illness (CDC-defined) diagnosis. The exposed group had reduced grey matter and hippocampal volumes, but these changes were not associated with changes in cognitive

function. Some significant correlations were observed between total white matter volume and some measures of executive function in the exposed veteran group. The Council observed that the relevance of these findings was uncertain, given the lack of any clinico-anatomical correlation and the fact that there was no significant group difference in the factor analysis-derived 'Haley syndromes' or in the prevalence of cases with 'chronic multisymptom illness' (CDC-defined). Chao et al¹⁰² re-examined the relationship between exposure and volumetric measurements of gross neuroanatomical structures in a different cohort of Gulf War veterans (64 exposed and 64 matched unexposed veterans) using cross-sectional neuropsychological and MRI data. There was even distribution of chronic multisymptom illness (CDC-defined) with 33 (52%) cases in each group. The study showed that exposed veterans had reduced total grey matter and white matter volumes compared to matched, unexposed Gulf War veterans. The authors reported no evidence of a dose-response relationship between cumulative exposure estimates and grey and white matter volumes. They did report that Gulf War illness/ chronic multisymptom illness status predicted grey and white matter volumes in the exposed veteran group. The Council noted that both of these studies had some significant methodological limitations, many of which were also noted by the authors. The most significant of these in the Council's view was that the exposure to sarin/cyclosarin was estimated rather than being based on objective measurements, and the estimation of exposure was done on a unit level rather than on an individual level.

303. In a survey of US Gulf War Naval construction battalion veterans by Haley and Kurt²⁹ discussed at [132], the authors stated that Haley-defined syndrome 2 (confusion-ataxia) was eight times more common in veterans who reported having 'experienced a likely chemical weapons attack' (relative risk (RR) 7.8, 95% CI 2.3-25.9) and four times more common in those who were 'located in the zone we designated "sector 7" in extreme north-eastern Saudi Arabia on 20 January 1991' (RR 4.3, 95% CI 1.9-10.0). Syndrome 2 was significantly more common in veterans who reported 'seeing the explosion of a suspected chemical land mine' (RR 5.6, 95% CI 2.3-13.6), but this finding did not remain significant in a logistic regression analysis after controlling for 'perceived chemical weapons attack' and 'presence in sector 7 on 20 January 1991'. The authors concluded that their findings showed that syndrome 2 was associated with several risk factors reflecting exposure to chemical weapons suggested that organophosphate nerve agent exposures "may have" contributed to illness in some of the ill veterans. A significant

dose-response relationship between amount of insect repellent used and syndrome 3 (arthro-myo-neuropathy) was demonstrated ($p < 0.001$), but only for some insect repellents (discussed at [374]). The authors stated that the synergistic effect of perceived chemical weapons exposure and the association with being in a certain area on the day independently implicated as a possible chemical weapons exposure are unlikely patterns to have resulted purely from recall bias and suggested causal effects. The Council, however, has previously noted the methodological weaknesses in this study making interpretation of the results problematic.

304. Sim et al¹⁹⁻²¹ discussed at [55], found the total number of general health symptoms reported in the month prior to the survey was significantly associated with self-reporting being in a chemical weapons area (95% CI 1.2-1.5, $p < 0.001$). Only 152 veterans self-reported being in a chemical weapons area compared to 1252 that reported they were not. A poorer SF-12 physical score and a poorer SF-12 mental score, were both associated with several Gulf War exposures, including 'being in a chemical weapons area', and 'military service experiences'. Functional impairment was defined as 'over the past two weeks', they had stayed in bed or at home all or part of any day because they did not feel well or as a result of illness or injury'. Functional impairment in the two weeks prior to the survey was associated with being in a chemical weapons area among several other exposures, as well as the level of military service experiences. The authors concluded that there was no objective exposure information to confirm self-reported exposure to chemical weapons. The authors stated that "people with health problems may be more likely to remember exposures, leading to a form of information bias"^{20(p398)}. As previously noted, the Council considered these studies to be methodologically strong, as they used objective health assessments rather than relying solely on self-reported symptoms and exposures.

305. Heaton et al¹¹² examined the association between modeled estimates of sarin/cyclosarin exposure levels and volumetric measurements of gross neuroanatomical structures in Gulf War veterans (13 exposed and 13 unexposed veterans) recruited from the Devens Cohort Study, with varying degrees of possible low-level sarin/cyclosarin exposure. Gulf War veterans whose units were located within ('exposed') and outside ('unexposed') the Khamisiyah hazard area in March 1991 were studied. MRI images of the brain were analysed using morphometric techniques, producing volumetric measurements of white

matter, gray matter, right and left lateral ventricles, and cerebrospinal fluid. Binary comparisons of sarin/cyclosarin exposed and unexposed veterans revealed no significant differences in volumetric measurements of discrete brain tissues. However, linear trend analyses showed a significant association between higher levels of estimated sarin/cyclosarin exposure and both reduced white matter (Adj. parameter estimate 4.64, $p < 0.0001$) and increased right lateral ventricle (Adj. parameter estimate 0.11, $p = 0.0288$) and left lateral ventricle (Adj. parameter estimate 0.13, $p < 0.0001$) volumes. The authors concluded that the findings suggested a subtle but persistent CNS pathology in Gulf War veterans “potentially exposed” to low-levels of sarin/cyclosarin. The Council did not place much weight on this paper due to the small number of cases, nor could the findings be extended to chronic multisymptom illness.

306. The Iowa Persian Gulf Study Group¹¹⁷ conducted a cross-sectional telephone interview to assess the prevalence of self-reported symptoms and illnesses among Iowa Gulf War veterans and to compare these rates with the prevalence of these medical and psychiatric conditions among Iowa non-Gulf War military personnel. A total of 4886 study subjects were randomly selected from one of four study domains (Gulf War regular military, Gulf War National Guard/Reserve, non-Gulf War regular military, and non-Persian Gulf War National Guard/Reserve) of which 3695 (76%) completed a telephone interview. Both study groups reported similar total doses of vaccinations, use of pyridostigmine bromide, and exposure to some potentially hazardous agents. The National Guard/Reserve personnel reported “higher rates” of exposure to smoke/combustion products, pesticides, sources of infectious agents, psychological stressors, and sources of lead from fuels than the regular military personnel. The authors found that the relationship between self-reported exposures and conditions suggested that no single exposure was related to the medical and psychiatric conditions among Gulf War military personnel. The Council noted the methodological issues with studies that rely on self-reported data. Furthermore, this study did not specifically focus on chronic multisymptom illness.

307. Kang et al¹⁸ conducted a cross-sectional study discussed at [86], and reported that in 277 Gulf War veterans who had all of the four symptoms (blurred vision, loss of balance/dizziness, tremors/shaking, and speech difficulty, i.e., suspected cases) 42.3% self-reported exposure to nerve gas compared to only 4.6% controls. The authors

concluded the study was limited by the fact that the cluster of four symptoms identified as a “neurologic factor” was based on self-reported data, which may be subject to reporting or recall bias. Furthermore, the Council has previously noted significant methodological limitations with this study discussed at [86].

308. Kelsall et al²² as discussed at [88], found the total number of health symptoms self-reported in the month prior was significantly associated with ‘being in a chemical weapons area’ (95% CI 1.2-1.5). The authors concluded that more than 10 years after the Gulf War, Australian Gulf War veterans reported all symptoms and some medical conditions, including psychological (particularly PTSD), skin, eye, and sinus conditions “more commonly” than a comparable group of ADF personnel. The authors also stated that increased reporting of symptoms and medical conditions by Gulf War veterans did not appear to be due to over-reporting or participation bias. Associations were shown between total number of self-reported symptoms in the month prior and several exposures experienced in the Gulf War, including immunisations, prophylactic medications, chemical exposures, and stressful experiences during their deployment, but there did not appear to be a unique single exposure associated with increased symptom reporting. The Council has previously noted the methodological strengths of this study (the use of objective health assessments).

309. Wolfe et al¹⁰⁰ examined data collected two years after return from the Gulf, from a cohort of Gulf War veterans who returned through Fort Devens Reunion Survey, a longitudinal study of 2949 US Army Active, Reserve and National Guard soldiers representing the second assessment of a group. The purpose of the study was to ascertain possible relationships between war experiences and subsequent health symptom reporting. The total study cohort involved 2119 veterans, and they were grouped into high (>5 symptoms), moderate (1-5 symptoms), and no symptoms. There were 275 veterans with >5 symptoms, 836 veterans with 1-5 symptoms and 1008 with no symptoms. In the final multivariate regression model after back-ward elimination, a significant association between exposure to ‘poison gas’ and increased reports of health symptoms (OR 6.3, 95% CI 1.2-33.3). The authors noted that self-reported exposure to poison gas remained significantly predictive of increased health symptom reporting even when people with presumptive PTSD were excluded from the analysis. The Council noted

the potential for recall bias in this study as a methodological limitation, as well as the self-reported nature of the data and the absence of objective health assessments.

310. McCauley et al¹⁰¹ evaluated the prevalence of past and current self-reported symptoms known to be associated with exposure to these chemical warfare agents. In a cross-sectional telephone survey of US Gulf War veterans, 1779 (516 non-deployed; 653 Khamisiyah; and 610 non-Khamisiyah veterans) were included in the analysis. The veterans in the Khamisiyah group were potentially exposed to nerve agents as they were within a 50 kilometre radius of the Khamisiyah Ammunition Storage Point between 1-15 March 1991. Of the 653 veterans in the Khamisiyah group, 162 individuals reported that they had been involved in or watched the Khamisiyah operations and 405 reported they had not been involved or had not watched. The Khamisiyah – witness sub-group relative to the Khamisiyah non-witness sub-group were more likely to report that during the first two weeks after the ground war they experienced numerous health symptoms. The authors reported that all but three of the symptoms (rashes, hoarseness, and skin blisters) have been described as effects of exposures to organophosphate chemical warfare agents and all symptoms described as low-dose-exposure first effects were elevated in the Khamisiyah subgroup. When the 162 veterans who had been involved in or watched the Khamisiyah detonations were compared with the Khamisiyah veterans who had neither been involved in nor watched the detonations, significant increases were found for several symptoms such as 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, tiredness, or weakness (OR 1.8, 95% CI 1.2-2.6), and depression (OR 1.6, 95% CI 1.1-2.4). However, no significant differences were seen in current health symptoms or those experienced in the two-week period in which the Khamisiyah detonations occurred between the Khamisiyah group and the non-Khamisiyah group. However, there were significant differences in symptom reporting by the subset of veterans who had been involved in or watched the Khamisiyah detonations. The Council felt that the results of this study needed to be viewed with some caution, given the methodological limitations involved (such as the reliance on self-reporting and the inherent potential for recall bias).

Studies of Other Military Groups

311. Page¹¹⁸ conducted a telephone survey of 4022 US military volunteers for a 1955-1975 program of experimental exposures to chemical agents (including sarin and other

anticholinesterases) at Edgewood, Maryland. The current health of those exposed to sarin and other anticholinesterase agents (chemical test) was compared with that of men exposed to no active chemicals (no chemical test) and to two or more other types of chemical agents (other chemical tests). This study comprised of 1339 subjects exposed to anticholinesterase agents, 1324 subjects not exposed to any chemical agents and 1359 subjects exposed to two or more chemical agents other than anticholinesterase agents. There were only two statistically significant differences: volunteers in anticholinesterase agent tests reported fewer attention problems than those in other chemical tests and greater sleep disturbance than those in no chemical tests. In contrast, volunteers who reported exposure to civilian or military chemical agents outside of their participation in the Edgewood program reported many statistically significant adverse neurological and psychological effects, regardless of their experimental exposure. The author concluded that the health effects of self-reported, non-experimental exposure (which are subject to recall bias) were greater than the health effects of experimental exposure. The Council noted that the study did not apply directly to chronic multisymptom illness, and that it was a good example of the inherent methodological limitations of studies that rely on self-reporting of exposures with no objective correlating measures.

Studies of Japanese People Exposed to Sarin

Background

312. The Council considered a number of studies¹⁰³⁻¹¹⁰ conducted on Japanese people exposed to sarin. These papers provided important insights into effects of sub-lethal exposure to sarin and longer-term effects of sarin exposure that caused possible long-term neurological effects of sarin exposure, but did not look specifically at the constellation of symptoms, which are part of chronic multisymptom illness. The Council noted the level of exposure was based on the severity of symptoms and serum cholinesterase measurements.

313. There have been two terrorist attacks in Japan using sarin, one in June 1994 and the other in March 1995. A number of long-term follow-up studies of the exposed population have attempted to document the long-term health issues that may have relevance to the illnesses experienced by Gulf War veterans potentially exposed to nerve gas.¹⁰³⁻¹¹⁰

314. In 1994, a sarin gas attack occurred in a residential area in the city of Matsumoto, Japan exposing approximately 600 people, of which 58 were hospitalised and seven died.¹⁰³ It was estimated that 12 litres of 70% sarin solution¹¹⁰ was released by terrorists using a heater and fan, and a remodelled truck. In 1995, 11 plastic bags containing fluid with 30% sarin¹¹⁰ was placed in five cars on three separate Tokyo subway lines and poisonous vapours were released from the bags exposing more than 5000 people and resulting in 12 deaths.¹⁰⁹ In both incidents, those exposed included residents who were brought to hospitals exhibiting acute cholinergic symptoms consistent with exposure.¹¹⁰ Rescue workers and healthcare staff working with people poisoned also complained of sarin poisoning symptoms such as eye symptoms, headache, throat pain, dyspnoea, nausea and dizziness.¹¹⁰

Reports, Reviews and Meta-analyses

315. In 2007, Yokoyama¹⁰⁶ presented his observations in a review of neurobehavioral and neurophysiological effects in Tokyo subway sarin poisoning cases as well as in pesticide users (tobacco farmers) in Malaysia concerning Green Tobacco Sickness. In sarin cases, significant neuropsychological effects and balance dysfunction were observed six-eight months after the sarin exposure. The author also found an increased incidence of PTSD and mood disorders. Studies on pesticide users revealed that organophosphorus and dithiocarbamate affected peripheral nerve conduction and postural balance.

316. In 2006, Yanagisawa et al¹¹⁰ conducted a review of the two terrorist attacks with the nerve agent sarin that affected people in Matsumoto and Tokyo, Japan in 1994 and 1995. In Matsumoto, there were seven deaths, 56 people admitted to hospitals; 208 visited outpatient clinics; and 277 with symptoms who did not seek medical attention. In Tokyo, there were 12 deaths. No subjects demonstrated the long-term effects of sarin on cognitive functions such as dementia on medical checks up to 10 years later. Electroencephalography (EEG) abnormalities were noted in four asymptomatic subjects and resolved within five years. Neuropathy and ataxia were observed in small number (less than 10 percent) of victims, and resolved, in most cases, between three days and three months. Leukocytosis and high serum creatine kinase (CK) levels were common. Hyperglycaemia, ketonuria, low serum triglyceride, hyponatassaemia were observed in severely affected victims. PTSD was documented in less than 8 percent of people exposed after five years. However, psychological symptoms continued in victims of both

incidents. The Council considered this study to have several strengths, including actual exposure to nerve agents and the use of objective health assessments.

Cohort and Case-control Studies

317. To clarify the later sequelae of sarin poisoning in 1999 Nakajima et al¹⁰³ conducted a cohort study on all 2052 Japanese people who inhabited an area near the sarin release site in the centre of Matsumoto. With a response rate of 60.3%, 1237 persons (318 'victims' who had either been given a diagnosis of sarin toxicity or had muscarinic and/or nicotinic symptoms immediately after the sarin incident and 919 'non-victims' who had no symptoms immediately after the sarin incident) completed the survey and acted as an internal control group. The 1237 people who inhabited the area around the release site, up to three years later documented a number of chronic non-specific symptoms (asthenopia, fatigue, asthenia, blurred vision, headache and slight fever) in exposed subjects, though the exact pathophysiology of these symptoms was not established.¹⁰³ The authors acknowledged that PTSD was not excluded as a cause for some of the symptoms. One case of early polyneuropathy due to sarin exposure was identified. Delayed peripheral neuropathy has been reported in humans after organophosphorus insecticide exposure,¹¹⁹ although, this effect has apparently not been described in humans after nerve agent exposure.¹⁰³ The Council noted polyneuropathy has not been a recognised feature in the studies of chronic illness of Gulf War veterans and not in the chronic multisymptom illness criteria.

318. In 2001, Kawana et al¹⁰⁹ conducted a five year follow-up study of 582 sarin exposed people given emergency care at St Luke's hospital on the day of the Tokyo subway attack, 283 (48.6%) responded in 1997; 206 (35.3%) responded in 1998; and 191 (32.8%) responded in 2000. A significant number of subjects continued to experience non-specific unexplained physical symptoms, many of which were similar to the Matsumoto cohort (eye strain, dim vision, difficulty focusing, tiredness, fatigue, muscle stiffness and headache) and psychological after effects, which were attributed to the development of PTSD. The authors concluded that the psychological after-effects remain an important cause for ongoing persistent somatic symptoms even up to five years following the sarin attack in the Tokyo subway. The Council considered this study to have several strengths, such as the long-term follow up nature of the study and the use of objective health

assessments. However, the emphasis of the study was on PTSD and as such did not specifically focus on chronic multisymptom illness.

319. In 2007, Yamasue et al¹⁰⁵ conducted a MRI morphometric and diffusion tensor imaging study of 38 of the 582 people (as described by Kawana et al¹⁰⁹) treated for sarin toxicity and 76 matched healthy control subjects. The study demonstrated a significant regional volume reduction in insular cortex, neighbouring white matter and hippocampus, as well as disruption of white matter integrity in exposed subjects which showed positive correlations with serum cholinesterase levels at the time of hospitalisation, a marker of sarin exposure.¹⁰⁵ The authors commented that the mechanism by which acute sarin exposure induces brain volume loss has yet to be clarified. It was not possible to rule out the possible effects of psychological trauma on brain structure, however the positive correlation with serum cholinesterase and not with psychological symptoms suggested that psychological stress was not a confounding factor. The authors concluded that this study might be the first in vivo human evidence of a relationship between single acute exposure to sarin and long-lasting morphological changes in specific brain regions. They also suggested that the increased sensitivity to internal bodily status in the victims may be related to these morphological brain changes. The Council noted that the relevance of these changes in relation to chronic multisymptom illness is uncertain.

320. In two studies in 1998 by Yokoyama et al^{107, 108} of 18 exposed subjects performed six to eight months after sarin exposure, significant abnormalities of psychomotor performance, evoked potentials, and balance dysfunction, as demonstrated on posturography (females only), as well as an increased incidence of PTSD were found. After controlling for the effects of PTSD, changes in only one (digit symbol test) of the nine neurobehavioral tests were significant.^{107, 108} The authors concluded that abnormalities on the digit symbol test and posturography may have been caused directly by acute sarin poisoning, with many of the other changes being linked to PTSD. The Council noted that while cognitive impairment is a feature of chronic multisymptom illness, balance dysfunction is not.

Cross-sectional Studies

321. In 2005, Miyaki et al¹⁰⁴ performed a seven year follow-up of 36 Transit Authority staff exposed to sarin in the Tokyo subway attack. Of the 36 transit staff, 23 were exposed and

13 were referents. To assess a dose-response relationship, subjects were classified into high or low exposure groups; 5 subjects were classified as 'high exposure' as they were hospitalised immediately after the poisoning and 18 were 'low exposure' as they attended hospital as outpatients. Sarin-exposed subway workers performed poorer on one neuropsychological test than the referent group in a dose-dependent manner, in spite of the relatively low number of participants and seven-year interval after exposure. No significant differences were found on other neurobehavioral tests and stabilometry (posturography). The authors concluded that there was a chronic, statistically significant decline of one aspect of psychomotor function in subway staff seven years after exposure to sarin in the Tokyo subway sarin attack. By merging with previous data, the decline of memory function also proved statistically significant in the multivariate analysis. There were no measures of daily or occupational functioning. The positive dose-response dependent relationship and consistency of these findings suggested a causal relationship between exposure to sarin and the development of long-term health effects, however, the positive finding was only found in one of five neuropsychological test items. The Council found this to be weak evidence of an overall association.

Council's Conclusions on Studies Concerning Chemical and Biological Weapons:

Overall Quality of the Available Sound Medical-Scientific Evidence

322. In summary, the follow-up evaluations of individuals exposed to sarin in Japanese terrorist attacks provided convincing evidence to indicate that sarin exposure, at levels sufficient to cause acute symptoms, was associated with persistent symptoms and central nervous system effects in a subset of those exposed. A limited number of chronic neurobehavioral, imaging and neurophysiological abnormalities have been demonstrated in subjects following sarin gas exposure. Some of these abnormalities may have been explained by the co-existence of PTSD. Demonstration of similar abnormalities in veterans would need to be established before an aetiological link can be proposed and these studies provided no evidence to suggest that chronic effects of sarin exposure can occur in the absence of acute exposure symptoms. Haley et al^{70, 98} implicates chemical warfare agents and sarin in particular, for those people genetically predisposed as risk factors and co-factors respectively. Golomb has previously suggested that exposure to acetylcholinesterase inhibitors more generally, including the ingestion of pyridostigmine

bromide may “account for some or perhaps much of the excess illness seen in Gulf War veterans.”⁶²

323. Nine studies examined the association between exposure to chemical and biological warfare and the development of chronic multisymptom illness or symptoms of ‘Gulf War illness’.^{28, 44-46, 53, 70, 87, 98, 99} The Council noted that three papers^{44, 45, 99} used the CDC definition for chronic multisymptom illness to examine the association between exposure to chemical and biological warfare, and two demonstrated significant associations.^{44, 45} Six papers used other definitions of ‘Gulf War illness’.^{28, 46, 53, 70, 87, 98}

324. Wolfe et al⁴⁵ found a significant association between chronic multisymptom illness and exposure to chemical odour. Unwin et al⁴⁴ found significant associations between chronic multisymptom illness and self-reported exposure to hearing chemical alarms sounding and the use of NBC suits for all three cohorts in the study (Gulf War, Bosnia and Era cohorts). Gray et al⁴⁶ found exposure to ‘fumes from munitions’ was significantly associated with ‘Gulf War illness’ (Gray-defined). Spencer et al²⁸ found combat-related conditions (which included working in areas where chemical warfare agents were found or stored) was significantly associated with ‘Gulf War illness’ (PEHRC-defined and CDC-defined for chronic multisymptom illness). Lucas et al⁵³ reported a statistically significant association between ‘Gulf War illness’ (Lucas-defined) and self-reports of ‘chemical suit use’. Haley and Tuite⁹⁸ demonstrated significant associations between ‘Gulf War illness’ (Haley-defined) and veterans who ‘had been in areas where the chemical nerve agent alarms sounded’. Haley et al⁷⁰ demonstrated that ill Gulf War veterans who met the ‘Gulf War illness’ had lower levels of PON1-Q, the isoenzyme that most protects from damage by chemical nerve agents including sarin.

325. Blanchard et al⁹⁹ found no significant association between chronic multisymptom illness and ‘exposure to munitions explosion in Khamisiyah’. Proctor et al¹¹⁵ found a significantly higher rate of chronic multisymptom illness in a low-to-no exposed group than in groups with more exposure. Steele⁸⁷ found no significant association between being ‘notified of proximity to Khamisiyah demolition site’ and ‘Gulf War illness’ (Kansas-defined and CDC-defined chronic multisymptom illness). The Council noted that the measure of exposure used in the studies are poor proxy measures of chemical weapons exposure.

326. No studies documenting acute sarin exposure symptoms in Gulf War veterans have been identified. There were no reports of troops exposed to doses great enough to cause “first noticeable effects”, which would set off chemical alarms and cause visible signs of the acute cholinergic syndrome. There were no medical reports by the US Army Medical Corps at the time of the release that were consistent with signs and symptoms of acute exposure to sarin.¹⁴ The information was consistent with the absence of reports of acute cholinergic symptoms. Furthermore, it remains unknown whether chronic neurological effects of sarin can occur in the absence of acute exposure symptoms.¹⁴
327. There seem to be no objective data on Chemical Warfare Agents uptake into the body.
328. Genetic variability in the ability to metabolise organophosphate compounds and pyridostigmine bromide has been proposed to explain susceptibility to toxin exposure in Gulf war veterans⁷⁰ but other studies do not support the association.^{72, 73}
329. With respect to the study by Haley et al⁶¹ that measured brain blood flow with SPECT in ill Gulf war veterans, the group differences and subject numbers were small, so the Council considered that these changes would need to be validated in a larger study with appropriate controls. The diagnostic factor analysis used by this group has not been validated by other investigators. If validated, these findings could suggest a mechanism but would not establish an aetiology.⁶¹
330. The sensitivity of the M8A1 chemical warfare agent alarms are consistent with ground level air concentrations of sarin around 0.11 mg/m³ or higher. Except for the fact that soldiers in northern Saudi Arabia wore protective suits, it was suggested by Tuite and Haley⁹⁷ that miosis and dyspnoea would have been evident.⁹⁷ It was then argued that some sarin exposure occurred by inhalation and skin absorption, and with subsequent low-level exposure which varied geographically. This argument is reasonable since there is a one-two minute delay between the presence of the chemical warfare agents and alarm¹¹¹ and the detection of around 0.11 mg/m³. However, there were no modelled data per se.⁹⁷ The concentrations were inferred from known M8A1 sensitivity and symptoms that suggested mild cholinergic stimulation (stomach cramps, urge to urinate or defecate).^{97(see Ref4)} However, it was acknowledged that the symptoms might have been side effects of pyridostigmine bromide (see the Councils comment regarding side effects at [152]).

331. Those veterans who reported believing that they had been in an area where chemical warfare agents had been used were also likely to have been co-exposed to the uncomfortable use of respiratory protective equipment and protective clothing. When so many co-exposures are present, it can be difficult to identify with certainty which exposure may be the most important one concerning causation. This was the case with several of the general health outcomes, where associations were found for many exposures and experiences in the Gulf, rather than just one of these exposures.²⁰ It was also unclear whether the actual exposure or the belief in exposure is the most important aetiological factor.²⁸ As Spencer et al²⁸ claimed:

We previously described our reasons for not using the perceived exposure to chemical and biological weapons, and we believe that unless or until the Department of Defense provides more evidence of the presence of chemical or biological agents in the Gulf War, the report of these exposures is most likely to be a surrogate for stress and fear of a potential attack.^{28(p1054)}

Summary

332. The Japanese studies only documented long-term toxicity in human subjects after sarin gas exposure in those subjects who developed acute exposure symptoms. These studies did not consider chronic multisymptom illness specifically, however, some neuropsychological effects and some balance dysfunction were among the symptoms discussed. Studies examining possible long-term toxicity from low-level exposure during the Gulf War have failed to convincingly demonstrate acute exposure symptoms.

333. The Council concluded that the evidence of long-term health effects occurring after acute exposure to sarin gas during the Gulf War was limited and there was no objective human evidence to support the hypothesis that chronic toxicity can occur in the absence of acute exposure symptoms. Much of the evidence was based on self-reported and hypothetical exposures in the absence of any definitive exposure evidence.

THE COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE FACTOR(S) FOR CHEMICAL AND BIOLOGICAL WEAPONS

334. In summary, based on the criteria described above at [34-37], the Council considered that the SMSE was insufficient to point to a link between the development of chronic multisymptom illness and exposure to chemical and biological weapons. On that basis,

the SMSE does not indicate a reasonable hypothesis connecting chronic multisymptom illness to chemical and biological weapons. As the Council has concluded that the reasonable hypothesis test was not established, the balance of probabilities test necessarily could not be met.

PESTICIDES

Applicant's Contentions concerning Pesticides

335. The Applicant cited Mackness et al,¹²⁰ Hotopf et al,⁷³ and Costa et al^{121, 122} which it contended, “found a link to the activity levels of PON1 which suggested a person’s genetic predisposition could make some people more susceptible to organophosphate toxicity.”

336. The Applicant contended that Mackenzie Ross et al¹²³ findings “suggest a relationship may exist between low-level exposure to organophosphates and impaired neurobehavioral functioning and these findings have implications for working practice and for other occupational groups exposed to organophosphates such as aviation workers and Gulf War veterans.”

337. The Applicant cited Mackenzie Ross et al¹²⁴ (cited by the RMA and elsewhere as Ross et al) systematic and meta-analytic review of 14 studies reporting neurobehavioral problems following low-level exposure to organophosphate pesticides. The Applicant stated the review found the, “majority of well-designed studies found a significant association between low-level exposure to organophosphate and impaired neurobehavioral function. The association is consistent, small to moderate in magnitude and concerned primarily with cognitive functions such as psychomotor speed, executive function, visuospatial ability, working and visual memory.”

338. The Applicant also cited studies by Unwin et al,⁴⁴ Spencer et al,²⁸ and Schumm et al⁶⁰ and contended that they found risks for chronic multisymptom illness associated with pesticide exposure.

339. The Applicant contended that Kelsall et al^{24(p816, Table5)} and Suadicani et al⁴⁹ found the number of ‘neurological symptoms’ reported were significantly associated with pesticide exposure and use of insect repellents.

340. The Applicant also cited studies by Haley and Kurt,²⁹ Gray et al,⁴⁶ (p1040-41, Table7) and Spencer et al²⁸ and contended that they found risks for 'Gulf War illness' associated with pesticide use or exposure.

341. In her testimony to the RMA, Professor Beatrice Golomb cited reports by Cecchine et al¹²⁵ and Winkenwerder for the US Department of Defense.¹²⁶ Professor Beatrice Golomb stated that pesticides, with health concerns emphasising that carbamate and organophosphate are both acetylcholinesterase inhibitors,¹²⁵ were extensively used, sometimes beyond acceptable use.¹²⁶

The Council's Assessment of the Sound Medical-Scientific Evidence concerning Pesticides:

Background

342. The available evidence on pesticides focussed primarily on exposures experienced during the Gulf War, and except for a few papers^{28, 44, 72, 125} was not specific to chronic multisymptom illness. Further, available papers often referred to pesticides in general, and not to particular substances or groups of related compounds.

343. In these Reasons, the Review Council focussed on those papers that described those pesticides, which reported symptoms associated with chronic multisymptom illness as defined in the SoPs.

344. For this summary, exposures to chemical warfare agents were not explicitly considered, although some nerve agents were initially developed as pesticides, and there may be interactions. Similarly, pyridostigmine bromide, a cholinesterase inhibitor, was considered separately, but potentially may interact with pesticides, or become important for those with a genetic susceptibility – see section on combined exposures at [394-412].

345. During military operations, pesticides have been widely used as preventive health measures. Individual military personnel used personal pesticides such as DEET and permethrin, while wider area applications involved the use of a wide variety of pesticides such as organophosphates and carbamates. Applications involved the use of a wide variety of pesticides such as organophosphates and carbamates, and was generally carried out by the formal applicator and preventive medicine personnel.^{63, 126, 127} DEET was contained in personal use sprays and lotions. Clothing was often treated with

permethrin, and permethrin sprays were made available to continue protection after uniform washing etc. Tents and mosquito nets were also similarly treated.

346. Most of the available literature looked at Gulf War veterans, but the Council in their review looked not only at these but also at non-military exposures regarding chronic multisymptom illness symptoms.

Reports, Reviews and Meta-analyses

347. Of the available reports, reviews, and meta-analyses the Council considered the best evidence on exposure to pesticides was documented in the US Department of Defense Environmental Exposure Report on Pesticides¹²⁶ and the RAND Report by Fricker et al.¹²⁸ The Council also considered a meta-analysis by Ross et al¹²⁴ (also cited as Mackenzie Ross) provided the best evidence of neurobehavioral effects following low-level, long-term occupational exposure to organophosphates. The Council also paid particular attention to reports by the IOM,^{5, 11} a RAC report by Binns et al,¹ a RAND report by Cecchine et al¹²⁵ and reviews by Terry,¹²⁹ Golomb,⁶² Yokoyama,¹⁰⁶ Costa et al,^{121, 122} and Furlong.¹³⁰

348. In a large review for the US Department of Defense by Winkenwerder¹²⁶ commented that overexposure to pesticides may contribute to the development of unexplained illness in veterans, but they also argued that little actual objective exposure data were available, and also that few veterans actually sought medical help or treatment for acute exposure events. In the report, overexposure to pesticides was defined as “a chemical exposure sufficient to cause observable symptoms which have a reasonable potential to be detrimental to health.”^{126(TabA, p12)} Overexposure was not actually quantified or explained in further detail. The authors concluded that:

...overexposure to pesticides, particularly organophosphates and carbamates, may have contributed to the unexplained illnesses reported by some Gulf War veterans. However, there is little documentation that quantifies Gulf War pesticide overexposure and veteran interviews suggest that fewer than ten veterans sought treatment for pesticide exposures.^{126(Section6, p1)}

349. According to this US Department of Defense Exposure Report¹²⁶ at least 41 000 service members are thought to have been overexposed (observable symptoms which have a

reasonable potential to be detrimental to health) to pesticides during the Gulf War. But fewer than 10 sought medical treatment for pesticide exposures. Pesticide applicators were thought to have higher exposures, and to have been exposed to the more potent pesticides, however, only 3500-4500 individuals worked as applicators during the Gulf War.¹²⁶

350. Pesticide exposure during the Gulf War was the result of deliberate use (or misuse) by coalition forces, rather than occurring as a result of other contacts, e.g. pesticide residues from agricultural applications. The self-reported use and misuse of pesticides products was summarised in the RAND report by Fricker et al¹²⁸ of a 1999 telephone survey of 2005 Gulf War veterans. The authors concluded that they did not find clear evidence of widespread misuse of pesticides, however, there were limitations with recall bias and accuracy issues.

351. Ross et al¹²⁴ (also cited as Mackenzie Ross) reviewed the available evidence of neurotoxicity of low-level occupational exposure to organophosphates and reported the results of a meta-analysis of 14 studies. All studies addressed the issue of whether long-term, low-level exposure to organophosphates was associated with neurobehavioral deficits, but different populations of people were examined including chemical plant workers, greenhouse workers, pest control operatives, pesticide applicators (sheep dippers, fruit tree sprayers, crop sprayers). The authors defined this exposure as “repeated or prolonged exposure to doses, which do not produce recognised clinical symptoms of acute toxicity requiring medical evaluation or intervention.”^{124(p22)} This definition was particularly relevant to this review, since there was very little evidence of acute poisoning in veterans but considerable self-reported exposures to pesticides. This study found a significant association between low-level exposures to organophosphates in those occupationally exposed (mainly farmers and organophosphate workers) and impaired neurobehavioral and cognitive function, such as slowed reaction times, impaired fine motor skills, and in more severe cases deficits in executive function and memory. The analysis suggested that neurobehavioral problems developed over considerable time (years) and not after a single episode of exposure, with intensity and duration of exposure considered to be critical determining factors. The Council noted this meta-analysis was well conducted and considered the effects of publication bias. However, the methodological differences between studies made it difficult to assess the

precise nature of the relationship between exposure to organophosphates and neurobehavioral functioning. Additionally, actual exposure data were scant, with most of the exposures based on self-reporting and recall.

352. The 2003 IOM Volume 2: Insecticides and Solvents report⁵ reviewed the literature on the insecticides and solvents to which Gulf War veterans may have been exposed, and the long-term adverse health outcomes associated with that exposure. The IOM committee noted that the data for insecticide exposure in veterans of the Gulf War was inadequate and could not extrapolate from findings of published studies of occupational groups. The IOM committee found that two studies^{44, 131} of Gulf War veterans and chronic multisymptom illness (CDC-defined) found some associations with self-reported pesticide exposure. However, the IOM committee found the possibility of a type I (false-positive) error existed for both studies, in that both made multiple comparisons without adjustment for the number of comparisons. Also, the Council considered recall bias was a possibility as both studies used self-reports of exposure and no definitive conclusions can be drawn from these studies.⁵

353. In the 2010 IOM Volume 8: Update of Health Effects of Serving in the Gulf War report,¹¹ the IOM committee noted that:

Pesticides, including dog flea collars, were widely used by troops in the Persian Gulf to combat the region's ubiquitous insect and rodent populations, and although guidelines for use were strict, there were many reports of misuse. The pesticides used included methyl carbamates, organophosphates, pyrethroids, and chlorinated hydrocarbons. The use of those pesticides is covered in several reports ...however, objective information regarding individual levels of pesticide exposure is generally not available, and reports by individual veterans as to their use of and possible exposure to pesticides are subject to considerable recall bias. ^{11(p14)}

354. A RAC report by Binns et al¹ (discussed at [50-54]), stated that studies of Gulf War veterans consistently implicated only two wartime exposures as significant risk factors for 'Gulf War illness' the use of pyridostigmine bromide pills and use of pesticides during deployment. The authors stated that "...taken together, all available sources of evidence combine to support a consistent and compelling case that pesticide use during the Gulf

War is causally associated with Gulf War illness.”^{1(p225)} As above, this finding was based almost entirely on self-reported exposure.

355. In a RAND report by Cecchine et al¹²⁵ of the scientific literature of ‘Gulf War illnesses’ and pesticides, the authors concluded there was insufficient evidence to clearly define a causal link between self-reported pesticide exposure and increased likelihood of illness.”^{125(Ch9, p2)} The authors stated that the pesticide literature emphasised the importance of individual differences in susceptibility and these differences can play a pivotal role in determining rates of metabolism and clinical toxicity of acetylcholinesterase inhibiting agents.

356. Terry¹²⁹ conducted a review examining the functional consequences of repeated organophosphate exposure and the potential non-cholinergic mechanisms. The author concluded that notwithstanding the atypical findings as detailed in [348] where a large number of people were thought to be exposed and very few sought medical treatment, that low-level (subacute and subclinical) exposure might have occurred and there might be important (and potentially delayed) interactions between pesticides and other chemical compounds. The authors considered that there was also some evidence that organophosphates exert their toxicity beyond cholinergic mechanisms.¹²⁹

357. In a review of acetylcholinesterase inhibitors and ‘Gulf War illness’ by Golomb⁶² the author concluded there was a case for a causal connection of exposure to carbamate and organophosphates acetylcholinesterase inhibitors to illness in Gulf War veterans. She concluded that epidemiological studies reported a link between acetylcholinesterase inhibitors exposure and unspecified chronic symptoms (“excess illness”) in Gulf War veterans, and that the associations were generally strong. The Council noted that this study made very general findings, did not specifically address chronic multisymptom illness, referring instead to unspecified excess illness, which the Council felt was a vague and undefined term.

358. A 2006 review study by Yokoyama¹⁰⁶ discussed at [315], the author discussed his observations of neurobehavioral and neurophysiological effects in Tokyo, Japan subway sarin poisoning cases. The authors also considered pesticide users (tobacco farmers) in Malaysia concerning Green Tobacco Sickness. The review highlighted the organophosphate-related problems after acute exposure, including of possible peripheral

nerve damage (based on peripheral slowed nerve conduction deficiency velocities) and postural balance impairment issues, suggesting possible vestibulo-cerebellar dysfunction.¹⁰⁶ The Council noted the relevance of these findings to chronic multisymptom illness was unclear as these features are not part of the chronic multisymptom illness definition.

359. In an earlier review, Costa et al¹²¹ reviewed the role of PON1 in the detoxication of organophosphates and its human polymorphism. The authors discussed the high level of variation of gene expression within each genetic class in humans, together with their animal model studies indicated that it is very important to determine PON1 status as opposed to PON1 genotype alone. The authors concluded that in examining the population enzyme distribution plots, it was also clear that there are individuals within populations who never develop high levels of PON1 and “may” therefore be quite sensitive to the organophosphate compounds processed via pathways involving inactivation by PON1.

360. A later review by Costa et al¹²² discussed the relevance of polymorphisms in PON1 for modulating sensitivity to organophosphorus compounds. The authors stated that animal studies characterising PON1 polymorphisms have demonstrated the relevance of PON1 in modulating organophosphate toxicity and have indicated the importance of an individual's PON1 status (i.e., genotype and phenotype taken together) rather than genotyping alone. The direct confirmation in humans of the relevance of PON1 status in conferring susceptibility to organophosphate toxicity is still unclear. The authors noted that recent studies examining the involvement of PON1 status in determining organophosphate susceptibility of Gulf War veterans, sheep dippers, and individuals poisoned with chemical warfare agents are a step in the right direction, but that more studies are needed with better documentation of both the level of exposure and the consequences of exposure. The Council has previously noted the difficulty in correlating the findings of PON1 polymorphism studies with the chronic multisymptom illness SoPs.

361. In a review by Furlong¹³⁰ PON1 status and neurologic symptom complexes in Gulf War veterans was discussed. The author concluded, "...in a retrospective study of toxic exposures, it is difficult to determine the compounds to which individuals were exposed, as well as the level of exposure and the consequence of the exposure."^{130(p155)} The Council agreed with this, as it underscores the inherent methodological issues with most

of the studies considered in this review of chronic multisymptom illness, which often rely on self-reported exposures in the absence of objective and documented actual exposures.

Cohort and Case-control Studies

362. The Council reviewed studies by Spencer et al²⁸ and Lucas et al⁵³ which specifically examined chronic multisymptom illness or 'Gulf War illness' symptoms.

363. Spencer et al²⁸ discussed at [82], reported a significant association between self-reported 'use of insecticide spray on uniforms (permethrin) (OR 3.13, 95% CI 1.72-5.74) for 'Gulf War unexplained illness' (PEHRC-defined) and (OR 3.56, 95% CI 1.84-6.93) for 'Gulf War illness' (CDC-defined chronic multisymptom illness). The odds ratio for the association with self-reported 'use of DEET' was 2.68 (95% CI 1.52-4.74) for 'Gulf War unexplained illness' (PEHRC-defined) and was 3.33 (95% CI 1.78-6.25) for 'Gulf War illness' (CDC-defined), both significantly associated. After examining multiple factors potentially responsible for 'chronic multisymptom illness' symptoms in veterans, Spencer et al²⁸ found that after adjustment for stress (defined in two ways: psychological combat-related stress measured by the Keane combat score; and physiological heat-related stress, measured by the sun-exposure score), the odds ratios for 'multisymptom illness' associated with pesticide use (and other factors) all showed no significant association. The authors concluded that 'unexplained illness' in veterans was more associated with combat conditions rather than exposure to substances such as pesticides or pyridostigmine bromide (see detailed discussion at [82]). The authors did not report any interaction between repetitive insecticide use and the likelihood of unexplained health effects. The authors argued that it was unlikely that the many thousands of veterans with unexplained symptoms are suffering from neurotoxic effects of chemical exposure.

364. Lucas et al⁵³ conducted a case-control study discussed at [120], and reported binary exposures and their associations with health in Gulf War veterans showed a statistically significant association between fatigue and self-reported 'personal pesticide use' (OR 3.52, 95% CI 1.17-11.08) but not for self-reported exposure to 'pesticides on clothing'. The Council noted this was a small sample size and confounders such as occupation and location were not controlled for.

365. Haley et al⁶¹ conducted a case-control study discussed in [168]. All subjects underwent a brain scan following infusion of saline and >48 hour later a second scan following infusion of physostigmine in saline. The study showed some changes in brain function in Gulf War veterans following a cholinergic challenge. The authors concluded that Gulf War-associated chronic encephalopathy in a subset of veterans may be due to neuronal dysfunction, including abnormal cholinergic response, in deep brain structures. The Council noted the study had some methodological limitations, including small sample size and the absence of an objective link between pesticide exposure and resulting brain function changes.

366. In a case-control study by Tillman et al¹³² of 22 veterans meeting Haley-defined 'Gulf War syndromes' 1-3 and from 8 matched Gulf War veteran controls, who were deployed but not symptomatic, while they performed a visual three-condition oddball task where pictures of animals were the targets, scenes from the 1991 Persian Gulf War and weapons were the threatening distractors, and non-threatening pictures of objects, people, and nature were the standard stimuli. The authors reported the results suggested that the hyperarousal scores, which were more common in ill Gulf War veterans, were not due to PTSD and that the pattern of event related potentials was more consistent with changes in cholinergic or dopaminergic pathways. The Council noted the specific agents responsible for these putative neurotoxic effects were not identified in this study.

367. Individual susceptibility to chemical exposure, particularly genetic susceptibility, is a potentially important consideration that has been examined by several research groups. There have been several studies of the association between serum paraoxonase activity, which was partly genetically determined, and symptomatology in Gulf War veterans.⁷⁰ The findings and limitations of the nested case-control study by Haley et al⁷⁰ have already been discussed at [169].

368. Mackness et al¹²⁷ examined the potential link between organophosphate pesticide exposure and 'Gulf War syndrome' (15 neurological and other symptoms previously reported to be associated with 'Gulf War syndrome' – Haley-defined) with specific reference to the levels of PON1 in UK veterans and gender-matched controls (healthy non-Gulf War veterans). A total of 152 (61% response rate) Gulf War veterans with "self-reported 'Gulf War syndrome'" via a questionnaire (the median number of symptoms

was 5, range 3-13) and 152 healthy controls. PON1 hydrolyses organophosphates, rendering them into readily excretable compounds with no health effects. The authors found that there were lower serum concentrations of PON1 in Gulf War veterans self-reporting the presence of symptoms than in the matched control group, and that this was statistically significant (Mean (*M*) 75.7, µg/ml 18.1-351.3 compared to the controls *M* 88.2, µg/ml 34.5-527.4; $p < 0.0001$). This finding was independent of genotype. The authors speculated that a low PON1 level leads to suboptimal breakdown of organophosphates and that chronic multisymptom illness symptoms “may” result from this decreased enzymatic ability to handle organophosphate exposure. The Council noted the speculative nature of the conclusions reached in this study.

369. A study by Golier et al¹³³ found significantly lower adrenocorticotrophic hormone levels in Gulf war veterans without PTSD, compared to Gulf war veterans with PTSD and non-deployed veterans. In addition, the cortisol: adrenocorticotrophic hormone (ACTH) ratio was significantly associated with mood and cognitive symptoms in the Gulf war group as a whole, and self-reported exposure to pyridostigmine and pesticides was significantly associated with ACTH AUC (area under the curve) (as a marker of neuroendocrine system function) and self-reported exposure to pesticides. The authors concluded that the data provided evidence of hypothalamic-pituitary axis dysregulation and speculated that this abnormality may be explained by Gulf War deployment exposures. The Council noted this study did not specifically address chronic multisymptom illness and it was noted that mood and cognitive changes are only one of the three defining symptoms of chronic multisymptom illness.

370. In a study by Hotopf et al,⁷³ while PON1 activity was reduced in Gulf War veterans compared with military control groups, it was found to be independent of ill health. Genotypes did not explain the differences. The Council noted that this study did not assess chronic multisymptom illness, and as such felt that it was difficult to extrapolate the findings of this study to the discussion of chronic multisymptom illness.

Cross-sectional Studies

371. The Council reviewed studies by Unwin et al,⁴⁴ Gray et al,⁴⁶ Concato et al⁷² and Haley and Kurt²⁹ which specifically examined chronic multisymptom illness or ‘Gulf War illness’ symptoms.

372. In a self-reported cross-sectional survey of three UK military cohorts (Gulf War = 2735; Bosnia = 2393; and non-deployed Era = 2422) by Unwin et al⁴⁴ discussed at [123], significant associations between self-reported personal pesticides exposure and chronic multisymptom illness (CDC-defined) and all veteran groups were shown; Gulf War veterans (OR 2.2, 95% CI 1.9-2.6), Bosnia veterans (OR 1.8, 95% CI 1.5-2.2), and non-deployed Era cohort (OR 1.8, 95% CI 1.5-2.2). Additionally, significant associations for exposure to 'pesticides on clothing or bedding' and chronic multisymptom illness and all veteran groups were shown; Gulf War veterans (OR 1.9, 95% CI 1.6-2.2), Bosnia veterans (OR 1.7, 95% CI 1.4-2.2), and non-deployed Era veterans (OR 1.9, 95% CI 1.5-2.3). The study showed that veterans of the Gulf War were about three times more likely to fulfil criteria for chronic fatigue, post-traumatic stress reaction, or the chronic multisymptom syndrome (CDC-defined) criteria than those in the control cohorts, even after adjustment for confounders. The authors concluded that since associations of ill health with adverse events and exposures were found in all cohorts, they may not be unique and causally implicated in Gulf-War-related illness. As such, the Council noted that this study pointed to a lack of an obvious aetiological link between pesticide exposure and chronic multisymptom illness.

373. In a cross-sectional study based on self-reported symptoms by Gray et al⁴⁶ discussed at [129], Gulf War Seabee respondents were asked questions regarding their experience with 34 possible exposures during the Gulf War, only 4% self-reported that they were exposed to pesticides. For 3831 Gulf War Seabees and exposure to pesticides was significantly associated with 'Gulf War illness' (Gray-defined) in the saturated multivariable model (OR 1.73, 95% CI 1.11-2.68). There were no significant associations found between 'wearing a flea collar' or 'wearing a uniform that had been treated with insect repellent' and 'Gulf War illness'. The Council noted the methodological issues with this study in its discussion at [129].

374. In a survey of US Gulf War Naval construction battalion veterans by Haley and Kurt²⁹ discussed at [132], reported syndrome 1 (impaired cognition) was significantly associated with 'wearing pet flea and tick collars' (RR 8.2, 95% CI 2.9-23.5) although the numbers of veterans in the subgroups were small, the risk increased with the likelihood that flea collars were worn in contact with the skin: 7 cases of syndrome 1 in 229 veterans (3%) who never wore flea collars, 3 cases in 17 veterans (18%) who wore them but never next

to skin, and 2 cases in 3 veterans (67%) who sometimes wore them next to their skin (χ^2 for trend, $p < .001$). Syndrome 2 (confusion-ataxia) was not significantly associated with self-reported 'pesticide exposure'. Syndrome 3 (arthro-myoneuropathy) was significantly associated with greater use of 'insect repellent DEET veterans typically applied to their skin' (χ^2 for trend, $p < .001$). In a multiple logistic regression analysis, the association of syndrome 3 with the six-point index of the amount of repellent used held true for those who used government-issued repellent (Adj. OR 1.54, 95% CI, 1.17-2.03), but not for those who reported using Off! (Adj. OR 1.08; 95% CI, 0.79-1.46) or Avon Skin-So-Soft (Adj. OR 0.87; 95% CI, 0.64-1.18). They also found that reported arthro-myoneuropathy symptoms were associated with increased use of these chemicals. The self-reported nature of this study as a methodological limitation must be noted. However, the authors did attempt to control for the potential effect of recall bias. While not specific for chronic multisymptom illness factors, this study did report some evidence of an association between pesticides and the development of some symptoms that are relevant to chronic multisymptom illness (such as cognitive changes and musculoskeletal symptoms). The authors concluded that the findings support their hypothesis that wartime exposure to combinations of organophosphates and other cholinesterase-inhibiting similar chemicals produced forms of chronic organophosphate-induced delayed polyneuropathy (OPIDP) in Gulf War veterans. The authors considered that "different combinations of these chemicals interacting with the ages of the exposed veterans may explain the different clinical syndromes identified"^{29(p236)} in their factor analysis. However, the Council viewed these as speculative conclusions not substantiated by their data, which lacked actual objective measures of exposure. Furthermore, the Council noted that chronic OPIDP is not a feature of chronic multisymptom illness. The Council has previously noted the methodological limitations of this study.

375. In the cross-sectional component of the AGWVHS, Sim et al¹⁹⁻²¹ discussed at [55], examined multiple exposures including pesticides. The authors noted that there was "some limited epidemiological and animal evidence of impaired neurobehavioral performance after chronic low-level exposure to some organophosphates."^{20(p51)} Additionally, they noted that there was some evidence of long-term effects following asymptomatic exposure but that this evidence was controversial and not accepted by all. They also commented on the degree of uncertainty regarding which veterans may have actually been exposed to pesticides, the problematic nature of studies relying on self-

reporting and the confounding nature of multiple exposures in studied populations. Their findings relating to Australian Gulf War veterans found a significant association between self-reported symptoms and exposure to various substances including pesticides, insecticides and repellents. Pesticide and insecticide exposures were all significantly associated with poorer physical and mental health outcomes and some functional impairment. The Council noted the associations found in the study, but also noted the self-reporting nature of the exposures and the difficulty with multiple exposures.

376. A cross-sectional study by Kelsall et al²² discussed at [88], showed the total number of self-reported health symptoms was significantly associated with 'pesticide use' (95% CI 1.2-1.4) and 'use of insect repellent' (95% CI 1.1-1.3). An association between pesticide exposure, pyridostigmine bromide tablet use and symptoms of ill-health was demonstrated.²² The reliability of recall over time was also noted as an issue by these researchers, an issue also noted by the Council.

377. In another Australian study, Kelsall et al²⁴ discussed at [178], a postal questionnaire of self-reported current neurological type symptoms, medically diagnosed neurological conditions, and medical and chemical exposures were used and a neurological examination was performed as part of a physical assessment. The findings showed that, while neurological symptoms reported by veterans were associated with pesticide exposure, there was no objective evidence of physical signs of neurological disease or impairment. The authors concluded that the inconsistency between reported symptoms and physical evidence seen, may be due to a number of factors, including information bias including recall bias, related to increased neurological type symptoms reported by veterans. Many of the conclusions of other epidemiological studies of veterans' neurological health have been based solely on self-reported findings. The authors stated their study emphasised the importance of using objective physical signs in the future assessment of veterans. The Council considered that the use of objective medical assessments represented a strength of this study.

378. Glass et al²⁶ conducted a cross-sectional self-reported postal questionnaires to identify chemical and environmental exposures specifically associated with Gulf War. The study involved 1424 Australian male Gulf War veterans, and a comparison group of 1548 ADF male personnel who were in operational units at the time of the Persian Gulf War but who were not deployed to that conflict. The Council noted that self-reported pesticide

exposure amongst Australian Gulf War veterans was not rated to be different from other deployments, and in some cases significantly lower.²⁶

379. In a cross-sectional, self-reporting study by Reid et al⁷⁶ discussed at [180], of three military cohorts (Gulf War = 3531; Bosnia = 2050; and non-deployed Era = 2614), the prevalence of chronic fatigue syndrome and multiple chemical sensitivity and their association with exposures and psychologic morbidity was examined. In Gulf veterans, multiple chemical sensitivity was significantly associated with exposure to pesticides (Adj. OR 12.3, 95% CI 5.1-30.0). The authors reported that both syndromes were associated with high levels of psychologic morbidity. The authors noted that it was difficult to make a conclusion on causality. The Council noted that since multiple chemical sensitivity was not equivalent to chronic multisymptom illness factors, it was not possible to extrapolate the findings of this study.

380. In a cross-sectional telephone survey study by Bell et al¹³⁴ there was no significant associations found between self-reported symptoms and pesticide exposure (OR 5.6, 90% CI 0.81-38.5) and insect repellent use (OR 5.5, 90% CI 0.91-33.2) in a group of ill Gulf War veterans ($n = 14$) compared with healthy Gulf War veterans ($n = 10$). The study involved only a small sample (Gulf War veterans = 28 and Era veterans = 20) with an 86% and 85% response rate respectively. In a group of ill Gulf War veterans with chemical odour intolerance ($n = 9$) compared with healthy Gulf War veterans ($n = 10$) there was a significant association between pesticide exposure (OR 12.0, 95% CI 1.3-111.3) and insect repellent use (OR 12.0, 95% CI 1.1-136.8), although a small sample size was used resulting in very wide confidence intervals. The authors concluded that among Gulf War veterans, the subset with worse health associated with marked increases in chemical odour intolerance since their military service had a significantly higher odds ratio for exposure to multiple chemicals, notably wartime pesticides and insect repellent, than did comparison groups. The Council noted it was also difficult to extrapolate the findings of this study to the discussion of chronic multisymptom illness.

381. A Danish cross-sectional retrospective self-reported prevalence study by Suadicani et al⁴⁹ (discussed at [255]) found a significant association between neuropsychological symptoms such as memory impairment, fatigue and sleeping problems and brushing teeth using water contaminated with chemicals or pesticides ($p \leq 0.001$) and insecticide use against cockroaches ($p \leq 0.001$) in the bivariate analysis. No significant associations

were seen between exposure to pesticides or insecticides and the neuropsychological symptoms after adjustment in a multiple logistic model. The Council noted this study did not assess chronic multisymptom illness, however memory impairment/sleep disturbance and fatigue are included in the chronic multisymptom illness definition.

382. In a cross-sectional studies of UK Gulf War veterans, Cherry et al⁴⁷ found borderline significant associations for a possible marker of peripheral nerve damage with pesticide handling (OR 1.26, $p < 0.01$) in the logistic regression analysis (although confidence intervals were not provided). The authors argued that it was “biologically plausible” that pesticide exposure could affect the nervous system. They also noted that there was a lack of consensus regarding long-term exposure to low-levels of pesticide causing nervous system damage in the absence of an acute poisoning event and that their method of assessing possible nerve damage was yet to be validated. The Council noted that these results need to be balanced against the fact that peripheral neuropathy has not been documented in subjects with chronic multisymptom illness, nor is it a diagnostic feature of this condition.

Studies of Occupational Exposures

383. Baldi et al¹³⁵ investigated the hypothesis that exposure to pesticides could be related to neurodegenerative diseases (such as Alzheimer’s disease) in a prospective cohort study of 1507 French elderly (1992 - 1998). Lower cognitive performance was observed in subjects who had been occupationally exposed to pesticides. In men, the adjusted relative risks of developing Parkinson's disease and Alzheimer's disease and ‘occupational exposure’ assessed by a job exposure matrix were 5.63 (95% CI 1.47-21.58) and 2.39 (95% CI 1.02-5.63). The authors concluded that the results suggested the presence of neurologic impairments in elderly persons who were exposed occupationally to pesticides. It was notable that the median occupational exposure period was 28 years in this study. The Council noted several limitations with this study, in relation to the present review. These included the elderly cohort (and therefore not a population equivalent to the military veteran cohort in this review), the inability to measure actual exposure doses, the inability to link specific pesticides with the effects observed, the complex aetiology of Alzheimer’s and other forms of dementia, the long median exposure time (28 years) and the well-documented issues with self-reporting and recall bias. The presence of multiple confounders and limitations reduces the power of this study and

the Council did not find this a highly relevant study for the purposes of this review into chronic multisymptom illness.

384. Hernandez et al¹³⁶ noted that the association could work in reverse, with chronic exposure to pesticides lowering PON1 activity and the use of protective suits working in reverse. The Council noted the speculative nature of this conclusion, and therefore did not attribute much weight to this study.

Council's Conclusions on Studies of Concerning Pesticides

Quality of the Available Sound Medical-Scientific Evidence

385. Six studies examined the association between exposure to pesticides and the development of chronic multisymptom illness or symptoms of 'Gulf War illness'.^{28, 29, 44, 46, 53, 72} The Council noted that three papers^{28, 44, 72} used the CDC definition for chronic multisymptom illness to examine the association between exposures to pesticides, one demonstrated a significant association.⁴⁴ Six papers used other definitions of 'Gulf War illness'.^{29, 46, 53, 61, 127}

386. Unwin et al⁴⁴ found significant associations between chronic multisymptom illness (CDC-defined) and self-reported exposure to personal pesticides and pesticides on clothing or bedding for all three cohorts in the study (Gulf War, Bosnia and Era cohorts). Gray et al⁴⁶ showed a significant association for 'Gulf War illness' (Gray-defined) and pesticide exposure although no significant association was demonstrated for 'wearing a flea collar' or 'wearing a uniform that had been treated with insect repellent'. Haley and Kurt²⁹ found Haley-defined syndrome 1 (impaired cognition) was significantly associated with wearing flea and tick collars, syndrome 2 (confusion-ataxia) no significant associated with self-reported pesticide exposure and syndrome 3 (arthro-myoneuropathy) was found with greater use of insect repellent DEET. Lucas et al⁵³ found binary exposures and their associations with health in Gulf War veterans showed statistically significant association between fatigue and personal pesticide use but not for pesticides on clothing.

387. Spencer et al²⁸ found that after adjusting for stress, there was no statistically significant association between multisymptom illness (CDC-defined) and pesticide use (and other factors). Concato et al⁷² found long-term acetylcholinesterase activity of stored blood serum samples showed no significant association with deployment or symptomatology of chronic multisymptom illness (CDC-defined).

388. The available SMSE was in general inconsistent and not directly concerned with chronic multisymptom illness factors. The studies considered were generally limited in quantity and quality. The majority of the studies were based on self-reporting of both exposures and health outcomes, and as such are subject to issues with recall bias on the part of participants. There are also several studies that have examined combined exposures, making the detection of an independent link between pesticide exposure and chronic multisymptom illness challenging.¹²⁴ These were significant methodological limitations which make the interpretation of the results problematic at best.

389. The studies examined did not provide objective data on actual exposures to pesticides. Furthermore, the evidence generally failed to make any distinction between different types of pesticides and chemical agents. Since there are a great number of different pesticides (which are also often available in different forms or used in different applications), use of the general term “pesticides” in a given study made the analysis of findings difficult.

390. The available evidence considered in this Review does not point to an association between pesticide use and/or exposure and chronic multisymptom illness factors.

Summary

391. The occupational toxicity documented following “low-level” exposure (levels insufficient to cause acute toxicity) in farms and organophosphate workers provided the best example of possible toxicity, but this entity was manifested by cognitive impairment and peripheral neuropathy and these changes have generally developed over many years of exposure. Cognitive impairment was only one of the three symptom categories in the chronic multisymptom illness diagnostic criteria and peripheral neuropathy was not a feature of this diagnosis, so it was difficult to extrapolate the results of these studies to the chronic health problems of Gulf War veterans.

392. The exposures in Gulf war veterans have been almost all self-reported or based on geographical location during the war, and accurate dose-response relationships have not been established. The bias introduced by self-reporting has been discussed previously. No consistent association has been observed between exposure and the development of symptoms of chronic multisymptom illness, and as such it follows that it was not possible to make a case for a pesticide factor to be included for chronic multisymptom illness.

THE COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE FACTOR(S) FOR PESTICIDES

393. In summary, based on the criteria described above at [34-37], the Council considered that the SMSE was insufficient to point to a link between chronic multisymptom illness and exposure to pesticides. On that basis, the SMSE does not indicate a reasonable hypothesis connecting chronic multisymptom illness to pesticides. As the Council has concluded that the reasonable hypothesis test was not established, the balance of probabilities test necessarily could not be met.

COMBINED EFFECTS FOR PYRIDOSTIGMINE BROMIDE, PESTICIDES, SARIN, PYRETHROIDS AND DEET

Applicant's Contentions concerning Exposure to Combined Effects of Pyridostigmine Bromide, Pesticides, Sarin, Pyrethroids and DEET

394. While it was not in scope, the Council noted that the Applicant referred to several papers that concerned exposure to combined effects of pyridostigmine bromide, pesticides, sarin, pyrethroids and DEET. For completeness, the Council has considered combined exposures.

395. The Applicant cited Haley and Kurt²⁹ and Kurt¹³⁷ to support their contention of an association between chronic multisymptom illness and combined exposures.

The Council's Assessment of the Sound Medical-Scientific Evidence for Combined Effects for Pyridostigmine Bromide, Pesticides, Sarin, Pyrethroids and DEET:

Background

396. Potentially, large numbers of military personnel were repetitively exposed to low environmental levels of the chemical nerve agent sarin and pesticides such as organophosphates and carbamates, and pyrethroids, while also taking pyridostigmine bromide during the Gulf War. The interaction of these exposures has been raised as a possible factor in the aetiology of chronic multisymptom illness.

Reports, Reviews and Meta-analyses

397. Of the available reports, reviews, and meta-analyses, the Council considered the best evidence on exposure to combined effects for pyridostigmine bromide, pesticides, sarin, pyrethroids and DEET was documented in reports by the IOM.^{4, 11} The Council also paid particular attention to a RAC report by Binns et al,¹ and reviews by Golomb⁶² and Kurt.¹³⁷

398. In the 2000 IOM Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines report by Fulco et al⁴ the IOM committee found there was:

...available evidence is of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association in humans. This is true particularly when pyridostigmine bromide exposures occur in combination with other combat exposures.^{4(p253)}

399. In the 2010 IOM Volume 8: Update of Health Effects of Serving in the Gulf War report,¹¹ the IOM committee concluded “that human epidemiologic evidence was not sufficient to establish a causative relationship between any specific drug, toxin, plume, or other agent, either alone or in combination, and Gulf War illness.”^{11(p259)}

400. In the US RAC review that included both human and animal studies, Binns et al¹ (discussed at [50-54]) stated there was a lack of evidence from human studies, including the many epidemiologic studies of Gulf War veterans available to support whether or not ‘Gulf War illness’ was associated with the combinations of exposures used in the Gulf War.

401. In a review of the evidence relating ‘Gulf War illness’ to acetylcholinesterase inhibitors, Golomb⁶² stated that increasing evidence suggested excess illness in Gulf War veterans can be explained in part by exposure to organophosphate and carbamate acetylcholinesterase inhibitors, including pyridostigmine bromide, pesticides, and nerve agents. The author concluded that acetylcholinesterase inhibitors exposure satisfies Hill’s presumptive criteria for causality, but this did not imply that all illnesses in Gulf War veterans were the result of acetylcholinesterase inhibitors exposure. It may account for some of the excess illness. The Council noted the review did not specifically consider chronic multisymptom illness.

402. In a personal review, Kurt¹³⁷ proposed the hypothesis that “sub lethal exposures to combinations of drugs and chemicals in the Gulf War, augmented by hyper thermic stress and age susceptibility, caused the development of delayed-onset neurotoxic syndrome variants”,^{137(p525)} though no new evidence was presented and the only evidence for delayed onset of neurotoxic effects came from animal studies. As such, the Council did not attribute much weight to this paper, given that its conclusions were speculative and based on animal studies.

Randomised Control Studies

403. Roy et al⁶⁸ as discussed at [163] concluded that appropriately combined treatment with pyridostigmine bromide, DEET, and permethrin were remarkably well tolerated and without evidence of short-term physical or neurocognitive impairment. The Council noted this was a well-designed, short-term study, which showed no evidence of short-term toxicity.

Cohort and Case-control Studies

404. In a population based case control study by Spencer et al²⁸ discussed at [82], reported associations between pyridostigmine bromide and combinations of combat stress, heat stress, insecticides (permethrin), and insect repellents (DEET) were examined to determine whether any interaction effect was present. In the bivariate analyses the association between PEHRC-defined 'unexplained illness' case status and each individual exposure of interest (Keane Combat Score, heat/sun symptoms, use of insecticide spray, insect repellent, and pyridostigmine bromide) showed a statistically significant association. However, when adjusted for the effects of stress, the odds ratios for insect repellent, insecticide spray, and pyridostigmine bromide use all decreased as all pairs of exposures were significantly associated with one other (all $p < 0.001$). The authors stated the results indicated that the insecticide-pyridostigmine bromide synergistic effect found by others to be associated with the likelihood of having unexplained illness was not replicated in their study. The authors also stated the results provided evidence that 'unexplained illness' in Gulf War veterans was more highly associated with both physical and psychological consequences of conditions of combat rather than exposure to substances with potential neurotoxic effects, such as pyridostigmine bromide and insecticide repellents, and that such unexplained illness cannot be explained by any neurotoxic effects of exposures to chemicals that inhibit cholinesterase activity. The Council considered a weakness of the study was that the exposure assessment was relatively poor, and the subjective nature of the classification of exposure clusters. It seems this was done because the odds ratios were statistically significant for many of the exposure variables (e.g. degreasing machinery, heat stress etc.). The exposure clusters have many inherent assumptions and go beyond single exposure variable.

Cross-sectional Studies

405. In a survey of US Gulf War Naval construction battalion veterans by Haley and Kurt²⁹ discussed at [132], found Haley-defined syndrome 1 (impaired cognition) was associated with 'wearing flea collars'; syndrome 2 (confusion-ataxia) was associated with self-reported chemical weapons exposure the effects of perceived chemical weapons exposure and advanced adverse effects from pyridostigmine bromide were synergistic (Rothman S, 5.3; 95% CI 1.04-26.7); and syndrome 3 (arthro-myoneuropathy) was associated with greater use of DEET in ethanol applied during the war and with advanced adverse effects from pyridostigmine bromide. The authors concluded that the findings supported the hypothesis that wartime exposure to combinations of organophosphates and other cholinesterase-inhibiting chemicals produced variants of chronic organophosphate-induced delayed chronic neurotoxic syndromes in Gulf War veterans. Different combinations of these chemicals interacting with the ages of the exposed veterans may explain the different clinical syndromes identified in the factor analysis of symptoms found in their previous research.²⁹ However, the Council noted that such organophosphate-induced delayed neurotoxic syndromes are not a feature of chronic multisymptom illness.

In Vitro Studies

406. In an in vitro study by Wille et al¹³⁸ the interactions between human cholinesterases, DEET, pyridostigmine, malaoxon and chlorpyrifosoxon showed a weak inhibition of human acetylcholinesterase and human butyrylcholinesterase by DEET. The authors concluded that the "inhibitory potency of the tested cholinesterase inhibitors was not enhanced by DEET and it did not affect the regeneration velocity of pyridostigmine-inhibited acetylcholinesterase."^{138(p79)} The authors stated that there was no evidence of a synergistic effect of the tested compounds on human cholinesterases. The Council noted the in-vitro and mechanistic nature of this study and as such did not attribute much weight to it.

Council's Conclusions on Studies Concerning Combined Effects for Pyridostigmine Bromide, Pesticides, Sarin, Pyrethroids and DEET:

Overall Quality of the Available Sound Medical-Scientific Evidence

407. In studies of Gulf War veterans, potential exposure to a number of factors makes it difficult to determine whether any one single exposure or combination of exposures are

the cause of many veterans' illnesses.⁵ Compared to the diverse amount of literature related to effects of individual exposures, research on the effects of combinations of Gulf War-related exposures was limited. While some authors suggested the wartime exposure to combinations of organophosphates and other cholinesterase-inhibiting chemicals produced delayed neurotoxicity^{29, 137} others found no significant association.²⁸

408. There was only one study by Spencer et al²⁸ that used CDC definition for chronic multisymptom illness and the authors found no significant association. The authors, who excluded self-reports of possible chemical warfare agent exposure due to potential bias, concluded that 'unexplained illness' in Gulf War veterans was more highly associated with both physical and psychological consequences of conditions of combat rather than exposure to substances with potential neurotoxic effects, such as pyridostigmine bromide and insecticide repellents.

409. There were major limitations in the research, such as the nature of cross-sectional studies, recall bias, lack of consensus criteria, non-clinical assessments and poor objective evidence of exposures. Furthermore, in trying to articulate a possible model for chronic multisymptom illness using the research findings, combining factors was almost an acknowledgement that single factors have not risen to significance. In other words, if pyridostigmine bromide pills or pesticide exposure, by themselves as single factors, were convincingly linked to chronic multisymptom illness, there would have been no need to look at them in combination. Other studies were again based on surveys with the same methodological flaws as outlined previously. There were also a large number of animal studies, the findings from which cannot be extrapolated to the development of chronic multisymptom illness.

Summary

410. The mechanism of combined toxicities from multiple chemicals exhausting the enzymes that break down these compounds to produce neurotoxicity was biologically plausible, particularly in some of the animal studies, however, these studies need to be replicated in humans before this theory can be supported.

411. The studies on combined effects had numerous methodological flaws. They did not always directly investigate chronic multisymptom illness, nor did they primarily investigate a combination of factors as the study objective. Some studies could be

considered preliminary findings or studies that generate hypotheses. Appropriate studies that would reach qualification for SMSE have not been conducted.

THE COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE FACTOR(S) FOR COMBINED EFFECTS FOR PYRIDOSTIGMINE BROMIDE, PESTICIDES, SARIN, PYRETHROIDS AND DEET:

412. In summary, based on the criteria described above at [34-37], the Council considered that there was insufficient SMSE to point to a link between chronic multisymptom illness and combined exposures of pyridostigmine bromide, pesticides, sarin, pyrethroids, vaccines and DEET. On that basis, there was insufficient SMSE to indicate a reasonable hypothesis connecting chronic multisymptom illness to combined exposure to pyridostigmine bromide, pesticides, sarin, pyrethroids and DEET. As the Council has concluded that the reasonable hypothesis test was not established, the balance of probabilities test necessarily could not be met.

COUNCIL'S ANALYSIS OF THE NEW INFORMATION

413. As mentioned above, in conducting a review, the Council was unable to (and so did not) consider information which was not available to (not before) the RMA at the relevant times. However, having formed the view that there was nothing in the pool of information which pointed to the relevant association, and being mindful of the Applicant's comments, the Council considered whether in its view there was a basis for recommending to the RMA that it (the RMA) undertake a new investigation.

414. The Council has neither the capacity nor the jurisdiction to perform an investigative function, including undertaking a comprehensive literature search. However, because of the Councillors' specialist expertise in this kind of injury, disease or death, the Council was aware of some new information (**listed at B2 of Appendix B**) which it considered on a preliminary basis.

415. The Council considered the new information to determine whether, in the Council's view, it warranted the Council making any directions or recommendations to the RMA.

416. In the Council's view any such direction or recommendation should only be made by the Council if it formed the view that the new information comprised SMSE as defined in section 5AB(2) of the VEA being information which:

- was information epidemiologists would consider appropriate to take into account; and
- in the Council's view, 'touched on' (was relevant to) the contended factor; and could potentially satisfy the reasonable hypothesis and/or balance of probabilities tests (as appropriate; see paragraphs [11] and [12] above for the relevant associations).

417. The Council was not sufficiently persuaded of the matters in [416] to make any recommendations to the RMA concerning undertaking a fresh investigation.

DECISION

418. The Council made the declarations summarised in paragraphs 1 and 2 above.

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