



Specialist Medical Review Council

## **Declaration and Reasons for Decisions**

*Section 196W*

*Veterans' Entitlements Act 1986*

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**Re: Decision of the Repatriation Medical Authority not to make**

**Statements of Principles for Gulf War Syndrome**

Request for Review Declaration No. 32

1. In relation to the decision of the Repatriation Medical Authority (RMA) not to make Statements of Principles for **Gulf War syndrome**, the Council under s.196W(5)(b) of the Veterans' Entitlements Act 1986 (the VEA), the Council DECLARES that it is not satisfied on the balance of probabilities that Gulf War Syndrome is a particular kind of injury or disease within the meaning of the VEA, and accordingly the sound medical-scientific evidence available to the RMA is insufficient to justify the making of Statements of Principles in respect of Gulf War syndrome.

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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 B**.
3. Fundamental to Statement 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.<sup>1</sup>

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<sup>1</sup> The SMSE 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 Applicants referred, being information, which was not available to the RMA at the relevant times, and so 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 **two applications**. Of these two applications, one was from the Australian Gulf War Veterans' Association (Applicant 1), and the other from a veteran of the Gulf War (Applicant 2), both seeking review of the decision of the RMA not to create SoPs for Gulf War syndrome.<sup>2</sup> Applicant 1 contended that there was SMSE on which the RMA could have relied to create SoPs in respect to Gulf War syndrome,<sup>3</sup> and to include factors for:
  - a) 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 pesticides exposure (including N,N-diethyl-m-toluamide (DEET));
  - b) Psychological stressors.

### **COUNCIL'S DECISION ON THE SCOPE OF REVIEW**

8. The Council wrote to both of the Applicants and to 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

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<sup>2</sup> The term 'Gulf War illness' is frequently used interchangeably with Gulf War syndrome, as are a number of other terms; the Council has noted this at [78].

<sup>3</sup> The Council has used the term 'Gulf War syndrome' throughout this review, as this was the term used by the RMA.

particular regard to whether there was SMSE on which the RMA could have relied to create SoPs for Gulf War syndrome that would include factors for any or all of the following factors:

- a) 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 pesticides exposure (including DEET);
- b) Psychological stressors.

### **METHODOLOGY (THE AVAILABLE INFORMATION)**

9. 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, and not on individual ratings in the review. Papers referenced in these reasons are those that the Council considered were most relevant to the issues before it.
10. 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 James H. Binns,<sup>1</sup> 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**

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

### **APPLICANTS' SUBMISSIONS**

12. The first 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.
13. The second Applicant made a submission to the SMRC on 27 March 2015.
14. Both Applicants also made oral submissions complementing their written submissions at the Council's meeting on 17 August 2016.

15. Both Applicants included contentions in their submissions that the SMRC considered were being made on legal matters. As set out in s.196ZA of the VEA, the only submissions the Council can consider are those about information that was available to the RMA at the relevant times and which were judged by the RMA as being SMSE, and could have relied to create or amend either or both the SoPs. Therefore, the summaries below only reflect those aspects of the submissions that the SMRC understands concern the information that was available to the RMA. These are summaries only of the key contentions of the Applicants in respect to the information.

### **SUBMISSION – APPLICANT 1**

16. In summary, in respect to the medical science, the Applicant submitted that “Gulf War illness” is the term given to the condition by medical experts, health researchers, the US National Academy of Sciences, and the US Institute of Medicine (IOM).

17. The Applicant contended that there is sufficient evidence consistent with the requirements in s5AB of the Veterans Entitlement Act 1986, to create a Gulf War syndrome SoP.

#### *Accepted by Medical Researchers*

18. The Applicant referred to a study by Kang et al,<sup>2</sup> which it contended found evidence for a “unique Gulf War neurological syndrome” associated with various exposures.

19. The Applicant contended that, “many reputable authors<sup>3-6</sup> agree on a distinct core group of symptoms giving rise to clear case definitions for ‘Gulf War syndrome’, ‘Gulf War illness’ or ‘unexplained chronic multisymptom illness’ among Gulf War veterans. Subsequently many of these case definitions formed the basis of research that led many scientists to offer credible hypotheses on what is believed by medical science, to be the diseases/ illnesses aetiology.”

20. The Applicant contended that the US Research Advisory Committee on Gulf War Veterans' Illnesses (the RAC)<sup>1</sup> “...comprised eminent medical practitioners who formulated the ‘reasonable hypotheses’ of a distinct pattern of illness in Gulf War veterans.”

#### *Consensus*

21. The Applicant contended that several international researchers have authored peer reviewed medical scientific papers with definitions of ‘Gulf War syndrome’, ‘Gulf War illness’, and ‘Gulf War Unexplained illness’.<sup>2, 7, 8(p1040-41, Table7), 9(p1043-56), 10(p999, Table5)</sup>

## *Definitions*

22. The Applicant referred to the IOM 2014 report, Chronic Multisymptom Illness in Gulf War Veterans Case Definition Re-examined<sup>11</sup> and contended that in its report, the IOM authors:
- recognised chronic multisymptom illness as “an important cause of disability in Gulf War veterans.”
  - recognised “absence of an agreed case definition for chronic multisymptom illness could lead to diagnostic uncertainty and limit an attending physician’s ability to select appropriate and effective treatment plans.”
  - recommended to the US Department of VA that it classify this condition as Gulf War Illness. A title, the Applicant contended “...that very much recognises the unique key exposures which the IOM described as “an impressive array of biologic and chemical agents.”
23. In its application for review to the RMA (referred to the SMRC by the Applicant), the Applicant cited papers by Blanchard et al,<sup>12</sup> Golomb,<sup>13</sup> Binns et al,<sup>1(p27)</sup> Steele et al,<sup>14</sup> and Iannacchione et al,<sup>15</sup> to contend that:
- Gulf War Veterans have reported a range of symptoms at rates twice that of comparable era and elsewhere deployed veterans, these most often include some combination of: chronic headache, chronic fatigue, cognitive dysfunction, personality/ mood change, fibromyalgia/ muscle and joint pain, chronic multi-symptom illness, respiratory problems, gastrointestinal problems, irritable bowel syndrome, and or skin problems.<sup>16(p12)</sup>
24. The Applicant contended that there are three case definitions in general use to define ‘Gulf War illness’; Steele/ Kansas,<sup>10</sup> US Centers for Disease Control and Prevention (CDC),<sup>17</sup> and the Haley case definition.<sup>3</sup>
25. The Applicant contended that the Kansas case definition by Steele<sup>10</sup> uses “a pattern of morbidity, of moderate or multiple symptoms in at least three of the six defined groups and in the absence of diagnosed exclusionary conditions, was associated with deployment to the Gulf War and defined ‘Gulf War illness’ for purposes of the study.”
26. The CDC defines ‘chronic multisymptom illness’<sup>17</sup> in Gulf War veteran studies with a case definition as having one or more chronic symptoms from at least two of three categories

(fatigue, mood-cognition, and musculoskeletal). The Applicant contended that the usefulness of the CDC criteria was recently investigated and found to be a useful tool in assessing illness in Gulf War veterans.<sup>18</sup>

27. The Haley case definition<sup>3</sup> describes variants of ‘Gulf War illness’ as three apparently distinct Gulf War syndrome variants, syndrome 1, 2 and 3.

28. The Applicant contended that Professor Robert Haley had developed a diagnostic testing regime for the condition and describes ‘Gulf War illness’ in terms of three syndrome variants:

- “Syndrome variant 1 (‘impaired cognition’) was comprised of mild cognitive deficits, including distractibility, forgetfulness, depression and chronic fatigue (daytime sleepiness) – not limiting employment appreciably.
- Variant 2 (‘confusion/ataxia’) included reduced intellectual functioning, confusion, vertigo and disorientation, resulting in substantial limitations of employment.
- Variant 3 (‘central neuropathic pain’) involved chronic, widespread joint and muscle pains and other sensory abnormalities such as paraesthesia and numbness but, as with variant 1, carried little limitation of employment.”

### *Unique Exposures*

29. The Applicant contended there is, “... overwhelming medical scientific evidence reported by a number of experts, in a variety of peer reviewed journals, that Gulf War exposures, many unique to this conflict, are responsible for the illness and deleterious health symptoms reported in exposed veterans.”<sup>2, 7, 8(p1040-41, Table7), 9, 12(p70, Table1), 19-23, 24(p175, Table9), 25, 26</sup>

30. The Applicant also cited two new<sup>4</sup> papers<sup>27(p762, Table6), 28</sup> to support this contention.

### *Unique Symptomology*

31. The Applicant contended that Broderick et al<sup>6</sup> described ‘Gulf War illness’ as “a complex disorder affecting nervous, endocrine and immune regulation.” Using this hypothesis, Broderick conducted targeted research, which was able to demonstrate “an autoimmune component in Gulf War illness aetiology.”

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<sup>4</sup> New papers are addressed separately.



32. The Applicant cited Kelsall et al<sup>22</sup> to contend that Australian Gulf War veterans reported “increased incidences and a greater severity of symptom than their era, non-deployed counterparts.”

#### *Increased Risk of Amyotrophic Lateral Sclerosis*

33. The Applicant cited a number of papers, one new on increased risk of amyotrophic lateral sclerosis (ALS) for Gulf War veterans as evidence of unique symptomology.<sup>5</sup>

34. The Applicant contended that Horner et al<sup>29</sup> “found risk to Gulf War veterans of ALS is calculated as risk ratios (RR) = (1.1 - 2.7).”

35. Other available papers on ALS cited by the Applicant included Haley,<sup>30</sup> Weisskopf et al,<sup>31</sup> Miranda et al,<sup>32</sup> and Cox et al.<sup>33</sup>

#### *Brain Abnormalities*

36. The Applicant contended that Gulf War Syndrome is, “...probably an acquired brain injury from chemical exposure.”

37. The Applicant contended that, “research teams led separately by Haley and Baraniuk have used functional diagnostic magnetic resonance imaging (MRI) to show changes in brain matter volume in ill Gulf War veterans.

38. The Applicant cited:

- Wakil et al<sup>34</sup> who they contend found a significantly high incidence of hypothyroidism in a group of United Kingdom (UK) Gulf War veterans using the Gold Insulin Stress Test procedure.
- Haley et al<sup>3</sup> and Rayhan et al<sup>35</sup> discovered reduced brain volumes or other brain atrophy in functional MRI examinations.
- Parihar et al<sup>36</sup> whose results the authors say, “show the first evidence of an association between mood and cognitive dysfunction and hippocampal pathology

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<sup>5</sup> The potential increased risk of ALS (known as Motor Neurone Disease in Australia) in Gulf War veterans does not shed light on the cause of other chronic symptoms in Gulf War veterans. ALS is a well-defined disease with objective clinical and neurophysiological abnormalities, as distinct from the symptoms reported by Gulf War veterans. The Council notes there are SoPs for Motor Neurone Disease, which is an alternative name for ALS.

epitomized by decreased neurogenesis, partial loss of principal neurons, and mild inflammation in a model of GWI.”

#### *Decreased Paraoxonase (PON1) Activity*

39. The Applicant cited Mackness et al,<sup>37</sup> Hotopf et al,<sup>38</sup> and Costa et al,<sup>39</sup> which they 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.”
40. The Applicant contended that Furlong<sup>40</sup> found that Gulf War veterans “...were exposed to some compounds for which PON1 status (PON1192 genotype/phenotype) contributes to resistance, consistent with the genetic and pharmacological data on the PON1192 polymorphism.”
41. The Applicant cited Hernández et al<sup>41</sup> who they contended found that, “chronic exposure to pesticides might decrease PON1 activity and pinpoints the potential usefulness of monitoring PON1 activity in occupational settings where exposure to organophosphates occurs.”
42. The Applicant contended that Haley et al<sup>42</sup> “...demonstrated that compared to controls, ill veterans with the neurologic symptom complexes were more likely to have the R allele (heterozygous QR or homozygous R) than to be homozygous Q for the PON1 gene.” The Applicant also contended that, “a history of advanced acute toxicity after taking pyridostigmine was also correlated with low PON1 type Q arylesterase activity.” The authors suggested, “these findings further support the proposal that neurologic symptoms in some Gulf War veterans were caused by environmental chemical exposures.”

#### *Immune System Changes*

43. The Applicant contended Broderick et al<sup>6</sup> hypothesised ‘Gulf War illness’ is a disorder affecting the nervous, endocrine and immune systems. They stated that he had found that under exercise challenge, immune biomarkers were expressed indicative of an autoimmune component in ‘Gulf War Illness’ aetiology.

#### *Other Papers Referred to by the Applicant in its Submission to the RMA*

44. The Applicant cited:
  - Doebbeling et al<sup>43</sup> who they contended found increased prevalence of nearly every symptom assessed from all bodily organ systems among Gulf War veterans.

- Kelsall et al<sup>22</sup> who they contended found that Gulf War veterans had a higher prevalence of all self-reported health symptoms than the comparison group.
- Kang et al<sup>2</sup> who they contended found that Gulf War veterans, “had a cluster of symptoms consistent with neurological impairment.”
- Research by Broderick et al<sup>44, 45</sup> who the Applicant contended, “...found differences in the pathology of Gulf War illness sufferers compared to patients with chronic fatigue syndrome during exercise stress tests.”

45. The Applicant also referred to the Council, papers by Forbes et al,<sup>46</sup> Thomas,<sup>47</sup> Haley and Kurt,<sup>7</sup> Hannan et al,<sup>48</sup> Haley et al,<sup>3</sup> Steele,<sup>10</sup> Mackness et al,<sup>49</sup> Moss,<sup>50</sup> Blaylock,<sup>51</sup> Mackenzie Ross et al,<sup>52</sup> and Kurt.<sup>53</sup>

#### *New Papers*

46. The Applicant cited two new papers<sup>27(p762, Table6), 28</sup> to support this contention of unique exposure.
47. The Applicant also contended that there is new evidence pertaining to potential genetic links and exposures experienced in the Gulf War.
48. The Applicant referred to new information by O’Callaghan et al<sup>54</sup> and Zakirova et al<sup>55</sup> saying, “...the in vivo modelling in mice continues to provide compelling proof of the damage from the unique GW exposures veterans experienced.”
49. The Applicant also contended that Kasarskis et al<sup>56</sup> “found that veterans who developed ALS following Gulf War Service experienced a shorter ventilator free survival compared to non-deployed ALS controls.”
50. The Applicant contended that Craddock et al<sup>57</sup> showed “there is strong evidence emerging that there are distinct biomarkers present in the blood of sick Gulf War veterans which are potentially indicative of damage to the hypothalamic-pituitary-adrenal (HPA) axis.”
51. A full list of the Applicant’s new information is at **B2 of Appendix B.**
52. The Applicant concluded that:

The existence of Gulf War illness is well documented, as too are the characteristic symptoms that have been recorded and published in numerous epidemiologic and clinical investigations.

Gulf War illness is a complex of multiple overlapping symptoms that affect several interdependent biological systems. Studies have identified significant biological alterations in deep brain structure, cognitive function, and molecular level changes associated with the immune and neuroendocrine systems in sick veterans.

## **SUBMISSION – APPLICANT 2**

53. A submission was received from a Gulf War veteran on 27 March 2015, referring the SMRC to the following papers:

- Research Advisory Committee on Gulf War Veterans' Illnesses. Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations. November 2008. Washington, DC: U.S. Department of Veterans Affairs; 2008. Available from: [http://www.va.gov/RAC-GWVI/Gulf\\_War\\_Illnesses\\_links.asp](http://www.va.gov/RAC-GWVI/Gulf_War_Illnesses_links.asp)<sup>1</sup>
- Golomb BA.<sup>6</sup> A Review of the Scientific Literature as it pertains to Gulf War Illness. Volume 2: Pyridostigmine Bromide. Santa Monica, CA: RAND Corporation; 1999. Available from: [http://www.rand.org/pubs/monograph\\_reports/MR1018z2.html](http://www.rand.org/pubs/monograph_reports/MR1018z2.html)<sup>58</sup>
- The Applicant submitted that the IOM 2014 Chronic Multisymptom Illness in Gulf War Veterans: Case Definitions Re-examined report<sup>11</sup> "...stated that the condition should be referred to as Gulf War illness."

## **COMMISSIONS' SUBMISSION**

54. The Repatriation Commission and the Military Rehabilitation and Compensation Commission (the Commissions) made a written submission to the Council received on 17 March 2014.

55. In summary, the Commissions stated the view that numerous studies of veterans deployed in the 1991 Gulf War had demonstrated a significantly higher prevalence of a wide range of self-reported non-specific health symptoms and worse subjective health in those veterans than in comparison groups of non-deployed veterans.

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<sup>6</sup> The RMA accessed the summary only of this paper.

56. The Commissions contended that, “the possibility that such symptoms and health outcomes represent a unique “Gulf War syndrome” has been extensively investigated. However, the same symptoms occur commonly in non-deployed veterans, other groups and the general population and the types and patterns of symptoms are the same in all groups. There are no clinical examination or laboratory findings that can identify cases and a pathophysiological basis for the symptoms has not been established.”

57. The Commissions concluded that there is not an identifiable disease process that is specific to service in the Gulf War.

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

58. 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.

59. The Council's final decision on the SMSE for the review was that it should comprise the information listed in **B1 of Appendix B**.

60. 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'. However, given the Applicants' detailed submissions on the new information the Council has made some concluding observations regarding that information.

### **BACKGROUND**

#### *Definitions of Disease or Injury*

61. Section 5D of the Act defines disease and injury relevantly as follows:

**Disease** means:

- a) any physical or mental ailment, disorder, defect or morbid condition (whether of sudden onset or gradual development); or
- b) the recurrence of such an ailment, disorder, defect or morbid condition;

but does not include:

- c) the aggravation of such an ailment, disorder, defect or morbid condition; or
- d) a temporary departure from:
  - i. the normal physiological state; or
  - ii. the accepted ranges of physiological or biochemical measures;

that results from normal physiological stress (for example, the effect of exercise on blood pressure) or the temporary effect of extraneous agents (for example, alcohol on blood cholesterol levels);

[and]

**injury** means any physical or mental injury (including the recurrence of a physical or mental injury) but does not include:

- a) a disease; or
- b) the aggravation of a physical or mental injury.

62. The question of what constitutes a disease or injury for the purposes of determining a SoP under the Act is to be determined by the ordinary meaning of those words. While reference and regard may be had to ordinary dictionary definitions, medical dictionaries, and expert knowledge, ultimately, determining whether a condition is a disease as defined, the Council must conclude on the balance of probabilities whether or not the claimed condition is a 'disease' as used and understood in its ordinary meaning.<sup>7</sup>

63. Being familiar with the ordinary English meanings of the terms that are used in section 5D, the Council considered whether Gulf War syndrome is a disease or injury. In doing so, it had regard to its expert medical knowledge and internationally agreed concepts in considering whether Gulf War syndrome is a disease or injury.<sup>59</sup>

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<sup>7</sup> Comcare v Mooi (1996) 42 ALD 495 and MRCC v May (2016) HCA 19.

64. A disease is a disorder (a disturbance or departure - e.g., of an organ or body system - from normal balance or healthy function). In epidemiology, accurate diagnosis of a disease requires a case definition. A case definition is a set of criteria that must be fulfilled in order to identify a person as representing a case of a particular disease.<sup>60</sup> A case definition can be based on geographic, clinical, laboratory, or combined criteria or on a scoring system with points for each criterion that matches the features of the disease. In deciding whether to include or exclude cases in an epidemiological study, a case definition must be highly reliable and repeatable.<sup>60</sup>

### **RMA REASONS**

65. In its investigation, gazetted on 31 October 2012 and concluded on 14 May 2014, the RMA determined that there is no unique Gulf War syndrome that meets the definition of a "disease" or "injury" in section 5AB(2).

66. This conclusion is consistent with decisions made by the RMA following investigations into Gulf War syndrome in 1999 and 2010.

67. In developing SoPs the RMA can only act on SMSE as defined in section 5AB(2) of the Act. A SoP must be determined if there is SMSE that indicates a particular kind of injury, disease or death can be related to service. A SoP then must promulgate factors in respect of that kind of injury, disease or death. Obviously, if the conclusion is reached that there is not 'a particular kind of injury, disease or death', then no SoP can be made.

68. In its 2010 Statement of Reasons for not making SoPs for Gulf War syndrome,<sup>61</sup> the RMA concluded that for Gulf War syndrome:

...there is no consensus in the SMSE as to what may constitute a unique syndrome among Gulf War veterans. Numerous studies been published on the health of Gulf War veterans. These studies have been comprehensively reanalysed, and reviewed by the U.S. IOM in a series of monographs published since 2000. These reviews noted that, compared to non-deployed veterans, Gulf War veterans self-reported an increased frequency of a range of symptoms including fatigue, memory loss, confusion, inability to concentrate, mood swings, somnolence, gastrointestinal symptoms, muscle and joint pain and skin or mucous membrane complaints.<sup>61(p6)</sup>

69. The 2010 Statement of Reasons<sup>61</sup> noted that the IOM and others have grouped the symptoms reported in the Gulf War investigations under the heading "chronic multisymptom illness" for

the purpose of trying to determine whether they constitute a disease and investigating their relationship to potential causative factors. The IOM assessed the published papers that investigated the relationship between specific exposures and chronic multisymptom illness, and determined that there was inadequate evidence to support a relationship.<sup>61</sup>

70. In its 2014 Statement of Reasons,<sup>59</sup> the RMA cited the conclusions of the IOM 2014 report<sup>11</sup> that, "Gulf War veterans report more symptoms and with greater frequency and severity than non-deployed veterans or veterans who were deployed elsewhere, but the types and patterns are the same in all groups."<sup>59(p7)</sup>
71. Citing Gray and Kang<sup>62</sup> and Macfarlane et al<sup>63</sup> the RMA contended that, "the evidence does not indicate increases in the occurrence of any specific pathology or grouping of pathological signs, the development of new pathological disease entities or processes over time, or an increase in deaths in Gulf War veterans."<sup>59(p7)</sup> Citing Roy et al,<sup>64</sup> Wille et al,<sup>65</sup> Stevens et al,<sup>66</sup> Williams et al,<sup>67</sup> and Hornby et al<sup>68</sup> the RMA contended that "...the results of animal and human tests of different combinations of Gulf War agents indicate no significant long-term health effects."<sup>59(p8)</sup>
72. The RMA stated that the only report that has found a distinct illness, and supported the role of Gulf War service in contributing to this illness was the Binns Report,<sup>1</sup> which was released in November 2008, by the RAC, a body established to advise the US Department of VA. The RMA noted that the report, "... like the Institute of Medicine's monographs, was a review of existing information, but differed in that it paid less attention to the human studies, and focussed more on inferences from animal toxicology."
73. The RMA offers a possible explanations for the differing conclusions reached by the RAC and other researchers as:
  - The criteria used by the RAC for assessing causality, which were not made explicit in the report and therefore cannot be subject to rigorous scrutiny. In contrast, the IOM specified in its reports that it used the criteria described by Bradford Hill.
  - The apparently greater weight placed on animal studies by the RAC.<sup>61</sup>
74. In its 2014 Statement of Reasons<sup>61</sup> the RMA stated that it drew upon both the original research reports of Gulf War veterans (primarily from the US, UK and Australia), as well as the



IOM and RAC reports. The RMA contended that its conclusions are consistent with the IOM, based on the same body of information.

75. The RMA contended that “long-term follow-up of personnel who served in the Gulf War has not revealed any evidence of a deterioration in health or new illnesses emerging in this cohort almost twenty years since the Gulf War, as one might expect if symptoms were associated with clinically significant pathology.”<sup>61(p7)</sup>
76. In summary, the RMA contended that the available body of SMSE shows a lack of a specific pattern of symptoms, a lack of pathological signs or emerging illnesses or deaths, insufficient support for a plausible biological mechanism and insufficient support for a link to specific exposures. On this basis, the RMA concluded that it would not make a SoP for Gulf War syndrome.

## **INTRODUCTION TO THE MEDICAL SCIENCE**

77. Veterans who returned from service from the 1990 - 1991 Gulf War reported a larger number of and range of, physical and psychological symptoms than non-deployed veterans.<sup>11, 69</sup> The symptoms included, amongst others, fatigue, musculoskeletal problems, neurocognitive problems, respiratory complaints, skin problems, and gastrointestinal disturbances.<sup>11</sup> These common symptoms are sometimes referred to as ‘medically unexplained symptoms’. They are real and can be distressing, and patients often experience a sense of frustration and helplessness due to the lack of diagnosis or determined cause. They are termed “unexplained”, not because the symptoms are not real, but because there is no settled or obvious physical problem causing them.<sup>70, 71</sup>
78. Establishing agreement on the terminology to collectively define these unexplained health symptoms has been difficult. Over time, a number of terms have been used, often interchangeably, to describe the chronic unexplained symptoms reported by veterans of the Gulf War, including ‘Gulf War illness or syndrome’, ‘unexplained illness’, ‘medically unexplained symptoms’ or ‘medically unexplained physical symptoms’, and ‘chronic multisymptom illness’.<sup>11, 72</sup> For this reason, this review includes papers, which have utilised a wide variety of terms to describe unexplained health symptoms, including all those listed above in this paragraph.

79. To be able to characterise the clinical features, evaluate potential risk factors, and assist with clinical treatment, many attempts have been made to organise symptoms reported by Gulf War veterans into a disease case definition. A case definition is a set of criteria that must be met in order to identify a person as representing a case of a particular disease. A case definition can be based on clinical, laboratory, geographic or combined criteria, or on a scoring system with points for each criterion, that matches the features of the disease. A case definition must be highly reliable and repeatable, and should enable the separate delineation of closely related but different diseases. However, it has not been possible to establish diagnostic criteria for Gulf War syndrome that exclude well-recognised medical and psychiatric causes of chronic somatic symptoms, nor has it been possible to distinguish the various symptom-based conditions from each other. Specific diagnosis has not been possible because subjective criteria do not usually provide sufficient information for accurate and reliable diagnosis of a postulated disease.<sup>73</sup> A number of different methods, such as clinical evaluation and the statistical technique of factor analysis have been used in developing case definitions for research studies.

#### *Current Case Definitions*

80. A widely accepted consensus case definition for the symptoms reported by Gulf War veterans has not been established. A number of different case definitions have been developed (Haley,<sup>74, 75</sup> Kansas,<sup>10</sup> Portland,<sup>76, 77</sup> US VA,<sup>78</sup> and the CDC<sup>17</sup>) and they have utilised different terms such as Gulf War syndrome,<sup>74, 75</sup> Gulf War illness,<sup>10</sup> Gulf War unexplained illness,<sup>76, 77</sup> unexplained multi-symptom illness,<sup>78</sup> and chronic multisymptom illness.<sup>17</sup>

81. The 'Haley' case definition was developed to define 'multisymptom illness' in Gulf War veterans using clinical observation and exploratory factor analysis to identify symptom groups in two distinct US populations. The clinical case definition defined by Hayley et al<sup>74</sup> was developed for the US Department of Defense from existing military survey and registry data, and review of selected cases of illness in Gulf War veterans who remained on active duty in 1994. The case definition requires at least five of eight named symptoms to be present and requires the absence of a physician's diagnosis of other medical and psychiatric illnesses that could cause or explain the reported symptoms.

82. The exploratory factor analysis developed by Haley et al<sup>74</sup> was based on a survey of symptoms reported by US Gulf War Naval veterans from five different states and their association with a

clinically derived case definition of 'Gulf War syndrome'. The response rate was low (41%), meaning that non-response bias was likely in this study. This bias was confirmed in an analysis, which demonstrated a lower prevalence of self-reported illness in the non-responders. The final sample size was 249. Using standardised symptom questionnaires and a two-stage exploratory factor analysis, six syndromes (impaired cognition; confusion–ataxia; arthromyoneuropathy; phobia–apraxia; fever–adenopathy; and weakness–incontinence) were identified.

83. In order to validate the syndrome-like structure identified by exploratory factor analysis in the study above,<sup>74</sup> Haley et al<sup>75</sup> used the same questionnaire in a different cohort of 335 Gulf War veterans living in North Texas who had served primarily in active-duty US Army units. The findings suggested that the apparent syndrome structure of a single Gulf War syndrome with three variants might be found widely, and not just in the initial study of 249 veterans. The authors concluded that a confirmatory factor analysis in a different sample survey of Gulf War veterans was required. They recommended a study of a national randomly selected sample of deployed and non-deployed Gulf War veterans in which their methods of symptom measurement and syndrome definition would be utilised, to validate their proposed case definition. It was acknowledged that the case definition by Haley et al<sup>74, 75</sup> was developed and validated in relatively small samples, limiting its external validity. Using a large population-based study of 8020 Gulf War veterans, Iannacchione et al<sup>15</sup> in 2011 reported on a computer-assisted telephone interview survey designed to validate the case definition in a much larger and representative population. The response rate was 60%. The findings supported the usefulness of the original factor analysis-derived case definition of three primary syndromes. The authors concluded that the Haley case definition applies to the full Gulf War veteran population and has good characteristics for research.
84. The 'Kansas' case definition for 'Gulf War Illness' was developed by Steele<sup>10</sup> using a descriptive approach to defined symptom groups based on measures of correlation and comparisons between Gulf War veterans and non-Gulf War veterans. A population-based survey of 1548 Kansas residents who were Gulf War veterans and 482 non-Gulf War veterans who served elsewhere was conducted to determine excess health symptoms, and the prevalence and patterns of occurrence. Six domains were identified. A diagnosis of 'Gulf War illness' requires the presence of three of the six domains, and an absence of diagnosed exclusionary conditions (cancer, diabetes, heart disease, chronic infectious disease, lupus,

multiple sclerosis, stroke, or any serious psychiatric condition). Only people who had at least one moderately severe symptom or two or more symptoms within a group were considered to have a high level of symptoms in the group. The internal reliability of each symptom grouping was determined using Cronbach's alpha. Symptom groups were considered reliable constructs if they were associated with an alpha of 0.70 or greater; individual items were retained within symptom groups if they had item-scale correlations of 0.50 or greater. The authors concluded that Kansas veterans experienced substantially more health problems than did era veterans who did not serve in the war.

85. The 'Portland' case definition for 'Gulf War unexplained illness' was developed by Spencer et al<sup>76</sup> and Bourdette et al.<sup>77</sup> Bourdette et al<sup>77</sup> conducted a population-based case-control study of a mail survey of 1119 randomly selected US Gulf War veterans living in Oregon or Washington and clinical examinations on a subset of 244 cases and 113 controls responders. The response rate was low, at 55%. Cases were required to report at least one of the following types of complaints: musculoskeletal pain; cognitive-psychological changes, including memory loss, confusion, inability to concentrate, and mood swings and/or somnolence; gastrointestinal complaints; skin or mucous membrane lesions; or unexplained fatigue. This case definition for 'Gulf War unexplained illness' was previously defined by Spencer et al in 1998,<sup>76</sup> based on this case definition, was revised using factor analysis. The final case definition included three groups of health complaints (cognitive/psychological, fatigue, and musculoskeletal).
86. The 'US VA' case definition for 'unexplained multisymptom illness' was developed by Kang et al<sup>78</sup> using a structured follow-up health survey to collect health information among a population-based sample of 15 000 Gulf War veterans and 15 000 non-Gulf War veterans. The health survey was based on the 1995 National Health Survey cohort<sup>79</sup> initiated by US VA to evaluate the health of the 1991 US Gulf War veterans, 10 years after the baseline survey in 1995. The case definition includes a range of symptoms that are not adequately explained by conventional medical or psychiatric diagnoses, such as fatigue; muscle or joint pain; headaches; memory problems; digestive problems; respiratory problems; skin problems; or any other unexplained symptoms that may sometimes be diagnosed as chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, or multiple chemical sensitivity. The study reported that Gulf War veterans continued to report a higher prevalence of many adverse health outcomes, compared to non-deployed veterans.

87. The 'CDC' case definition for 'chronic multisymptom illness' was developed by Fukuda et al<sup>17</sup> using an exploratory clinical approach and factor analysis to identify case defining symptoms. To organise reported symptoms into a case definition, characterise clinical features, and to evaluate risk factors, a cross-sectional questionnaire survey was conducted of 3723 currently active volunteers, irrespective of health status or Gulf War participation, from four US Air Force populations. In addition, a cross-sectional clinical evaluation of 158 US Air Force Gulf War veterans was conducted. Three symptom categories were identified: fatigue; mood and cognition; and musculoskeletal, and symptoms had to include one or more from at least two of the categories, with no exclusion criteria for established medical or psychiatric illnesses that may account for some or all of the required symptoms. No physical examination, laboratory, or serologic findings identified cases. In addition, factor analysis was performed: an exploratory principal components analysis was performed on the first half of the subsample and a second confirmatory factor analysis on the second. Since both case definitions were comparable, the symptom-category approach was chosen over the factor analysis-derived version because the authors considered that it was easier to apply in a clinical setting. However, information from factor analysis was used to derive the final case definition. The prevalence of mild-moderate cases and severe cases of 'chronic multisymptom illness' was higher in Gulf War veterans compared to non-deployed veterans: 39% vs 14% and 6% vs 0.7% respectively. Severe illness was associated with Gulf War service, enlisted rank, female gender, and smoking. The authors concluded that among currently active members of four Air Force populations, a chronic multisymptom condition was significantly associated with deployment to the Gulf War. However, the authors concluded that the condition was not associated with specific Gulf War exposures and also affected non-deployed personnel.
88. Since the 'CDC definition' for 'chronic multisymptom illness' was first published in 1998, it has been widely used in the international medical literature, mostly for research purposes, and a number of modifications or variations of this case definition have been used. In Australia, Kelsall et al<sup>69</sup> conducted a study using a questionnaire and medical assessment of 1381 male Gulf War veterans and 1377 male comparison group members. Important comorbid physical and psychological disorders in Australian male Gulf War veterans with 'multisymptom illness' were identified.<sup>69</sup> Response rates were 81% and 57% in deployed and non-deployed veterans respectively. Using a modified version of the CDC definition for 'multisymptom illness', they found that 25.6% of male Gulf War veterans and 16% of a male military comparison group met criteria for multisymptom illness. Kelsall et al<sup>69</sup> found that 'multisymptom illness' was

strongly associated with psychiatric conditions, medically unexplained chronic fatigue, and poorer health-related quality of life, and was more likely to be associated with physical or functional comorbidities when these were based on reported rather than objective measures.

89. The Australian Gulf War Veterans Health Study by Sim et al<sup>80-82</sup> 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 Gulf War but had not deployed to that conflict. The response rate was 81% in Gulf War veterans and 57% in the control group. The definition of 'multisymptom illness' used in the baseline study<sup>80-82</sup> was the same criteria detailed by Forbes et al<sup>83</sup> and Kelsall et al.<sup>69</sup> The most consistent finding was that the Gulf War veterans had developed more psychological disorders than the comparison group in the time since the 1990 - 1991 Gulf War, with the greatest excess risk being for post-traumatic stress disorder (PTSD). The level of reporting of all general health symptoms was also higher in Gulf War veterans. Factor analysis revealed a group of arthro-neuro-muscular symptoms, which were reported in excess, but the pattern of symptom reporting in the two groups was similar, suggesting that Gulf War veterans did not have a unique symptom complex or cluster.

#### *Reviews of Current Case Definitions*

90. The IOM has over a number of years reviewed, evaluated and summarised the available scientific and medical literature regarding 'chronic multisymptom illness'. In the 2013 Gulf War and Health, Volume 9: Treatment for Chronic Multisymptom Illness report by the IOM,<sup>72</sup> the literature concerning treatment of 'chronic multisymptom illness' was reviewed. The IOM committee used a new definition of 'chronic multisymptom illness' based on the reporting of a spectrum of chronic symptoms experienced for six months or longer in at least two of six categories—fatigue, mood and cognition, musculoskeletal, gastrointestinal, respiratory, and neurologic. 'Chronic multisymptom illness' was described as a "serious condition that imposes an enormous burden of suffering on our nation's veterans."<sup>72(p1)</sup>
91. In the IOM 2014 Chronic Multisymptom Illness in Gulf War Veterans: Case Definitions Re-examined report<sup>11</sup> the IOM committee was charged with developing a case definition of 'chronic multisymptom illness' and to:

...comprehensively review, evaluate, and summarise the available scientific and medical literature regarding symptoms for CMI among the 1991 Gulf War Veterans.

...the committee will evaluate the terminology currently used in referring to CMI in Gulf War Veterans and recommend appropriate usage.<sup>11(p2)</sup>

92. The IOM report noted the long-term difficulty there had been in defining ‘chronic multisymptom illness’ and its similarities to previously identified post-war syndromes. The IOM report noted serious limitations in using factor analysis to define a “case”, and stated that it was insufficient on its own to define a case.<sup>11</sup> Despite the charge given to the IOM committee,<sup>11</sup> they concluded that the available evidence was insufficient to develop a new case definition of ‘chronic multisymptom illness’. The IOM committee pointed out that “evidence is lacking in the studies reviewed to characterize most elements of a case definition (for example, onset, duration, severity, and laboratory findings) with certainty.”<sup>11(p10)</sup>
93. The IOM<sup>11</sup> reviewed all major definitions of ‘chronic multisymptom illness’ and recommended that the CDC<sup>17</sup> and the Kansas<sup>10</sup> case definitions best captured the array of symptoms most commonly identified by the evidence and best reflected the symptom complexes reported by Gulf War veterans. The IOM report stated that the CDC case definition, which had been widely used by researchers, identified 29-60% of US Gulf War-deployed veterans as ‘chronic multisymptom illness’ cases depending on the population studied, whereas the Kansas definition identified 34% in the population studied (in Kansas Gulf War veterans). It found that the CDC definition had the greatest concordance with all the other definitions and was less restrictive than the Kansas definition. It was noted that, the CDC definition required fewer symptoms, did not have any exclusionary criteria, and might identify a case without physical symptoms. In contrast, the Kansas definition would define fewer veterans as cases.<sup>11</sup> While the IOM report stated that each definition has its strengths, for example the CDC definition’s inclusion of severity indicators and the Kansas definition’s exclusionary criteria, it concluded that neither definition had been sufficiently validated. The IOM committee noted that neither definition addressed all the key features of a case definition, such as symptom onset, duration, severity, frequency of symptoms, and exclusionary criteria. However, given the absence of a defined disease state against which to validate the definitions, the IOM committee recommended, “with some reticence, the use of the CDC and Kansas definitions as a framework for future research and treatment.”<sup>11(p9)</sup> It did not find that one of the case definitions was superior to the other.
94. In the IOM 2014 Chronic Multisymptom Illness in Gulf War veterans: Case definitions re-examined report,<sup>11</sup> the IOM committee was also charged with evaluating the terminology

used in referring to 'chronic multisymptom illness'. The IOM committee noted that although Gulf War veterans reported a larger range of symptoms, the type and pattern of symptoms also occurred in non-deployed veterans, suggesting, "no unique syndrome is associated with Gulf War deployment."<sup>11(p9)</sup> Despite this, and to capture both the geographic area and the unique experiences of this group of veterans, the IOM committee recommended the term "Gulf War illness" be used.

95. Among Government reports, the US Department of VA Research Advisory Committee on Gulf War Veterans' Illnesses (the Binns report<sup>1</sup>) stands out in concluding that 'Gulf War illness' is a serious condition that affects about one-quarter of US Gulf War veterans. Despite this strong conclusion, the report acknowledged that no case definition of 'Gulf War illness' has been widely accepted. The Binns report<sup>1</sup> concluded that the prevalence of 'multisymptom illness' in Gulf War veterans is in the order of 25-32% in excess of that in non-deployed veterans.<sup>10, 84-86</sup> Despite the acknowledgement of a lack of a case definition, the report recommended that a "well-constructed and clearly-described case definition" be used in future research. The Council considered that given the acknowledged lack of an accepted case definition, the Binns report<sup>1</sup> overstated the case for the existence of 'Gulf War illness'.

### *Summary of Case Definitions*

96. In summary, while a number of different working case definitions have been developed for the symptoms reported by 1990 – 1991 Gulf War veterans, a consensus for a case definition has not been widely established. The use of different case definitions among studies makes it difficult to compare results, and depending on the case definition used, the prevalence estimates vary greatly, as does the generalisability and validity of the findings. The Council noted that the recommendation for the use of the term 'Gulf War illness' rather than 'chronic multisymptom illness' by the IOM is inconsistent with most published literature and with previous IOM reports.<sup>87, 88</sup>

### *Discussion of Evidence for a 'kind of injury, disease or death' attributable to service in the Gulf War or to Specific Gulf War-related Exposures*

#### *Symptom-based Conditions*

97. Disease classification systems use various parameters to define and classify disease, including anatomical location, pathology, clinical presentation, and aetiology. For a relatively small



number of diseases, classification and diagnosis is made solely on the basis of self-reported symptoms that have been judged to be clinically significant.<sup>59</sup>

98. The RMA has created SoPs for a number of diseases that are defined based on self-reported somatoform symptoms, for which no objective diagnostic test is available. They include diseases based on single symptoms, such as tension-type headache<sup>89</sup> and migraine<sup>90</sup> and those based on multiple symptoms, such as fibromyalgia,<sup>91</sup> chronic fatigue syndrome,<sup>92</sup> irritable bowel syndrome,<sup>93</sup> somatic symptom disorder,<sup>94</sup> and most relevantly, chronic multisymptom illness.<sup>95</sup>
99. Symptom-based conditions such as fibromyalgia and chronic fatigue syndrome have been assessed in a number of population-based studies of Gulf War veterans<sup>17, 24, 47, 84, 96, 97</sup> and there have been several reports that Gulf War veterans are more likely than other veteran groups to report such symptom-based conditions.<sup>47, 84, 96, 97</sup>
100. Many symptom-based conditions share symptoms reported by Gulf War veterans. In a study by Buchwald and Garrity<sup>98</sup> there were three groups of patients, which were similar in demographic characteristics and the presence of specific symptoms. People with chronic fatigue syndrome and fibromyalgia frequently reported symptoms compatible with multiple chemical sensitivities. Likewise, 70% of people with fibromyalgia and 30% of those with multiple chemical sensitivities met the criteria for chronic fatigue syndrome. Others argue, that while some of the symptoms reported by veterans meet the case definition(s) for other chronic health conditions such as chronic fatigue syndrome or fibromyalgia, many symptoms are not explained by established medical diagnoses or standard laboratory tests.<sup>1</sup>

### *Symptom Reporting In Gulf War Veterans*

101. Extensive research has been conducted on whether the physical and psychological symptoms reported by Gulf war veterans constitutes a unique Gulf War syndrome. However, there are wide variations in the symptoms reported, and the range of symptoms experienced by many Gulf War veterans do not demonstrate a unique pattern or constellation of symptoms with hallmark characteristics to make a clear aetiology, diagnosis, or prognosis.<sup>1, 11</sup>
102. Although the symptoms reported by Gulf War veterans are not unique to Gulf War deployed veterans, they are reported at a higher frequency and severity in deployed veterans than in non-deployed veterans, those deployed elsewhere, or the general population.<sup>12, 17, 19, 20, 24, 43, 69,</sup>

<sup>80-82</sup> A large number of studies<sup>17, 43, 80-82, 99-106</sup> have described increased self-reported symptomology for Gulf War veterans without any objective signs on examination or repeatable pathological correlate.

103. Sim et al<sup>80-82</sup> found the level of symptom reporting among Australian 1990 - 1991 Gulf War veterans was higher than that in the comparison group, although the pattern of symptom reporting in the two groups was similar, with three similar factors identified in each group. This finding suggests that Gulf War veterans do not have a unique symptom complex or cluster.

104. Doebbeling et al<sup>43</sup> reported that the increased prevalence of nearly every symptom assessed from all bodily organ systems among the Gulf War veterans was difficult to explain pathophysiologically as a single condition. Identification of the same patterns of factor-analysis grouped symptoms among the deployed veterans and non-deployed controls suggests that the health complaints of Gulf War veterans are similar to those of the general military population and are not consistent with the existence of a unique Gulf War syndrome.

105. Coker et al<sup>99</sup> reviewed the clinical findings in the first 1000 veterans seen in the UK Ministry of Defence's Gulf War medical assessment programme to examine whether there was a particular illness related to service in the Gulf. There was a high prevalence of reporting of a number of symptoms and 19% of men had a psychiatric illness, most commonly PTSD. The authors concluded that there was no evidence of a single illness, psychological or physical, to explain the pattern of symptoms reported by 1990 – 1991 Gulf War veterans.

106. Blanchard et al<sup>12</sup> reported on a cross-sectional US National Health Survey of Gulf War era veterans and their families, performed 10 years after the end of the 1990 – 1991 Gulf War. A main aim of the paper was to compare 'chronic multisymptom illness' in Gulf War veterans with 'chronic multisymptom illness' in non-deployed veterans. The study used the CDC 'chronic multisymptom illness' definition. 'Chronic multisymptom illness' was twice as common in Gulf War veterans, but still affected 15% of non-deployed veterans. The patterns of physical health problems in Gulf War veterans and non-deployed veterans with 'chronic multisymptom illness' were very similar, except that Gulf War veterans with 'chronic multisymptom illness' had a higher prevalence of chronic fatigue syndrome that was statistically significant ( $p = 0.001$ ). Both Gulf War veterans and non-deployed veterans with 'chronic multisymptom illness' reported higher prevalence's of non-PTSD anxiety disorders,

anxiety disorders, major depression, nicotine dependence, alcohol dependence (Gulf War veterans only), and more than one psychiatric disorder during the year preceding the examination. Pre-war non-PTSD anxiety disorders and depression were strongly associated with 'chronic multisymptom illness' regardless of deployment status. Despite a greater prevalence of 'chronic multisymptom illness' among Gulf War veterans, the authors found that both groups with 'chronic multisymptom illness' had a similarly poor quality of life and had substantially more comorbid symptom-based medical conditions and psychiatric disorders than veterans had without 'chronic multisymptom illness'. 'Chronic multisymptom illness' was more prevalent among deployed veterans than among non-deployed veterans 10 years after Gulf War, and manifested similarly in both groups. The authors concluded that distinguishing Gulf War 'chronic multisymptom illness' from non-Gulf War 'chronic multisymptom illness' was impossible using the general medical and psychiatric data collected in this study.

107. Forbes et al<sup>183</sup> conducted a cross-sectional study of 1322 male Australian Gulf War veterans and 1459 non-deployed military personnel. Using exploratory factor analysis of 1322 Gulf War veterans on 62 symptoms, a reproducible factor solution with three moderately correlated factors was identified for the latent structure underlying the pattern of symptom reporting. A similar three-factor solution was found in the comparison group. The three factors identified in the Gulf War and comparison group were psychophysiological distress, cognitive distress, and arthro-neuromuscular distress. This finding suggests there was no unique pattern of symptoms affecting Gulf War veterans only.

108. Kroenke et al<sup>104</sup> conducted a large cross-sectional study in US Department of Defense Comprehensive Clinical Evaluation Program of 18 485 Gulf War veterans. The most common symptoms were joint pain, fatigue, headache, memory or concentration difficulties, sleep disturbances, and rash. Symptom onset was often delayed, with two-thirds of symptoms not developing until after individuals returned from the Gulf War and 40% of symptoms having a latency period greater than one year. The authors concluded a lack of any association between specific symptoms and self-reported exposures makes an illness-related to toxic exposure less likely and no clinically recognisable unique disease or syndrome was shown.

109. Salamon et al<sup>107</sup> conducted postal questionnaires of 5666 French Gulf War veterans (99.5% male) and clinical evaluation of 1008 French Gulf War veterans. The response rate was 54%. The most frequent symptoms described 10 years after the return from the 1990 – 1991 Gulf

War were headaches, neurological or psychological symptoms, and back pain. Apart from well-known symptoms associations (respiratory, neurocognitive, psychological and musculoskeletal syndromes), no other cluster was highlighted. When compared with the non-deployed veterans a specific Gulf War syndrome was not identified.

110. Gray et al<sup>8</sup> conducted a health survey of 17 559 US Naval Mobile Construction Battalions (Seabees) with a 68.6% response rate. Compared with other Seabees, Gulf War Seabees reported poorer general health, a higher prevalence of all 33 medical problems assessed, more cognition difficulties, and a higher prevalence of four physician-diagnosed multisymptom conditions: chronic fatigue syndrome, PTSD, multiple chemical sensitivity, and irritable bowel syndrome. Because these four multisymptom conditions were highly associated with one another, the authors aggregated them into a working case definition of 'Gulf War illness'. Among the 3831 (22% cases) Gulf War Seabee participants, multivariable modelling revealed that being female, a reserve, enlisted, and belonging to either of two particular Seabee units predicted meeting the case definition of 'Gulf War illness'. Twelve of 34 self-reported Gulf War exposures were mildly associated with meeting the definition of 'Gulf War illness', with exposure to fumes from munitions having the highest odds ratio (OR) (OR 1.9, 95% confidence interval (CI) 1.5-2.4). The authors concluded that while these data do not implicate a specific aetiologic exposure, they demonstrated a strong association with certain exposures and a high prevalence of self-reported multisymptom conditions.

111. When Fukuda et al<sup>17</sup> developed their symptom based case definition for 'chronic multisymptom illness' in 1990 – 1991 Gulf War veterans they concluded that the study population's risk of illness was not associated with dates, seasons, duration, number of deployments, or military occupational activities. The risk factors present among both deployed and non-deployed populations were present at higher intensity or greater frequency among Gulf War veterans. The authors concluded the distribution of cases among Gulf War veterans and non-deployed personnel could not be explained by risk factors unique to Southwest Asia.<sup>17</sup>

112. A number of studies<sup>2, 10, 15, 74, 75</sup> have concluded there is a distinct Gulf War illness or syndrome. In one of the early definitional studies reported in 1997 by Haley et al,<sup>74</sup> the authors concluded that clusters of symptoms of many Gulf War veterans represent discrete factor analysis-derived syndromes that appear to reflect a spectrum of neurologic injury involving the central, peripheral, and autonomic nervous systems. They identified an apparent

syndrome structure of a single Gulf War syndrome with three variants. Other findings have supported this conclusion, also based on self-reported symptoms and factor analysis, were reported by Haley et al<sup>75</sup> in 2001 and Iannacchione et al<sup>15</sup> in 2011 (discussed under case definitions, see [83]).

113. Steele's<sup>10</sup> 'Gulf War illness' case definition, based on a study of Kansas Gulf War veterans, and reported in 2000, requires reporting chronic symptoms in three of six domains. The author observed patterns, which suggested that excess morbidity among Gulf War veterans was associated with characteristics of their wartime service (discussed under case definitions, see [84]).

114. Kang et al<sup>2</sup> reported of a study to identify a syndrome unique to Gulf War veterans. The authors concluded there was a unique syndrome consisting of blurred vision, loss of balance/dizziness, speech difficulty, and tremor/shaking in deployed Gulf War veterans. A small proportion (2.5%, 277) of the Gulf War veterans had all of the four symptoms. They also reported exposures to several putative risk factors at three or more times higher rate than that of other Gulf War veterans. They had significant overlap with the criteria for PTSD. Several associated medical conditions were reported significantly more often by these Gulf War veterans than by other Gulf War veterans. The authors stated that the finding suggested a possible syndrome related to Gulf War deployment (discussed under case definitions, see [86]).

#### *Reviews of Symptom Reporting in Gulf War Veterans*

115. A number of reviews have been conducted and have found increased reporting of symptoms by Gulf War veterans but no distinct disease<sup>11, 47, 62, 108-114</sup> with only Binns et al<sup>1</sup> concluding there is a distinct Gulf War Illness/Syndrome (see [95]).

116. Gray and Kang<sup>62</sup> conducted a summary of 15 years of observations and research in four categories of studies: Gulf War veteran's healthcare registries; hospitalisation; outpatient; and mortality. A total of 149 728 (19.8%) of 756 373 US, UK, Canadian, and Australian 1990 – 1991 Gulf War veterans received health registry evaluations revealing a large number of symptoms and clinical conditions, but no suggestion that a new unique illness was associated with service during the Gulf War.

117. Bieliauskas and Turner<sup>108</sup> conducted a review of four studies,<sup>7, 19, 74, 115</sup> which they concluded had an apparent bias toward symptom reporting, small numbers of subjects for relevant comparisons, low response rates, and the employment of questionable logical and statistical procedures, in particular factor analysis. The authors' conclusion was that 'Gulf War illness' is not a unique illness.
118. In a commentary, Joellenbeck et al<sup>109</sup> reviewed 11 published studies using standardised epidemiologic criteria for assessing causality. A consistent association was found between deployments to the Gulf and self-reports of symptoms. No consistency was seen in physical findings or laboratory results. Strength of association varied with different study designs. Dose-response information was limited, because of the lack of quantitative data on exposures. Biological plausibility varied for different risk factors. Specificity of association was not seen. The authors concluded that frequency of self-reported symptoms were increased in US Gulf War veterans compared to other veterans of the same era, but specific causes of illnesses could not be ascertained.
119. Barrett et al<sup>110</sup> performed a review of 15 controlled research investigations on symptoms of Gulf War veterans. They concluded that research had been hampered by the difficulty associated with developing case definitions for symptom-based conditions without objective criteria, and by the lack of adequate exposure information. Symptoms attributed to Gulf War syndrome are seen in other non-veteran groups, and this suggests that Gulf War syndrome is not a unique illness.
120. Hyams et al<sup>111</sup> conducted a review of the health problems of Gulf War veterans in comparison to previous post-war illnesses from the period since the US Civil War. They concluded that although previous post-war illnesses have been characterised by similar symptoms, no single recurring illness that is unrelated to psychological stress was apparent. However, many types of illness were found among evaluated veterans, including well-defined medical and psychiatric conditions, acute combat stress reaction, PTSD, and chronic fatigue syndrome. The authors concluded that a similarity in all settings was that the post-war populations were "intensely scrutinized after experiencing an exceptional, life-threatening set of exposures" and that the studies were "unable to conclusively show causality, have been subject to reporting bias, and have lacked similar control populations."<sup>111(p1)</sup>

121. In 2001, Wessely<sup>112</sup> reported on a review of the literature 10 years following the 1990 – 1991 Gulf War. He concluded that Gulf War service had affected the symptomatic health of a large number of those who took part. At the same time, no firm evidence had emerged of either distinct biomedical abnormalities or premature mortality.
122. In a review, Hotopf and Wessely<sup>116</sup> concluded that methodological issues had been a major issues in epidemiological studies. The median response rate in systematic reviews had been 65%, and had been systematically higher in Gulf War veterans than in non-veterans. Ascertainment bias had also been an issue, in that, in many studies efforts to find Gulf War veterans were conducted with more vigour than efforts to contact controls. Other issues identified included recall bias, problems identifying suitable control groups, and defining the disease and symptom outcomes. The difficulties had arisen partly owing to the significant delay between the point at which veterans first identified symptoms and the reporting of epidemiological studies. The authors concluded that health surveillance should be routine for future deployments.
123. In 2008, Greenberg and Wessely<sup>114</sup> conducted a review on Gulf War syndrome and concluded there was no discrete illness/syndrome attributable to the Gulf War. They postulated that “after conflicts military personnel will always face some form of post-conflict syndrome and the nature of the threats experienced is likely to dictate the form the syndrome might take.”<sup>114(p1)</sup>
124. In 1995, the Persian Gulf War Coordinating Board<sup>113</sup> reported on a review of ‘unexplained illnesses’ among Desert Storm veterans. The most commonly reported unexplained complaints were chronic fatigue, rash, headache, arthralgia’s/myalgia’s, difficulty concentrating, forgetfulness, and irritability. The authors concluded these symptoms have not been localised to any one-organ system, and there had been no consistent physical sign or laboratory abnormality that indicated a single specific disease.
125. Thomas et al<sup>47</sup> reported in 2006 on a systematic review of 23 publications relating to a total of 14 primary study samples that compared prevalence of multisymptom conditions in both Gulf War veterans and non-Gulf veterans. They used a random-effects model in the meta-analyses to estimate summary odds ratios. Gulf War veterans were approximately three and a half times more likely than non-Gulf veterans to report multiple chemical sensitivity (7 studies, OR 3.56, 95% CI 2.03-6.24), chronic multisymptom illness (CDC-defined) (5 studies,

OR 3.62, 95% CI 2.75-4.76) or chronic fatigue syndrome (10 studies, OR 3.81, 95% CI 2.17-6.71). They also found strong statistical evidence of variation between studies in these results. The authors stated that the methodological quality of the studies varied, and that at least some of the association might be explained by response bias, measurement bias and confounding. The authors concluded that the review cannot shed light on any biological or socio-cultural mechanisms underlying the association but added to the increasing body of evidence that suggests veterans of military deployment are more likely to subsequently report a variety of poorly understood complaints including fatigue, pain and associated symptoms.

126. The IOM has published a number of reports between 2006 and 2014,<sup>11, 72, 87, 88, 117</sup> which have comprehensively reviewed the numerous studies published on the health of Gulf War veterans in an effort to understand the nature and causes of chronic symptoms experienced by this group. In the IOM 2014 Chronic Multisymptom Illness in Gulf War veterans: Case definitions re-examined report,<sup>11(p10-11)</sup> the IOM committee stated Gulf War veterans reported more symptoms and with greater frequency and severity than non-deployed veterans or veterans who were deployed elsewhere, but the types and patterns of symptoms are the same in all groups. This finding suggests that no unique syndrome is associated with Gulf War deployment.

127. In the IOM 2010 Gulf War and Health, Volume 8: Update of Health Effects of Serving in the Gulf War report<sup>88</sup> the IOM Update committee examined the strength of association between deployment to the Gulf War and various human health outcomes. The IOM committee critically examined the human exposure studies cited by Binns et al (the Binns report)<sup>1</sup> as evidence that pyridostigmine bromide and pesticides are causally associated with 'Gulf War Illness'. The IOM Update committee stated:

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



related problems could reasonably be expected to result from these putative exposures. Indeed, the committee concludes that many key questions remain unanswered. This is true both with respect to the underlying cause or causes of the multisystem illness complex experienced by so many of the Gulf War soldiers, and also with respect to the adequacy of the experimental studies that have addressed the potential contribution of any external agent to the development, course, or persistence of this perplexing disorder. The committee concludes that it is essential to keep in mind that other etiologic factors may also play a role, and research into this matter must continue. The committee also concludes that it is possible that the specific cause(s) of the many and diverse symptoms reported by the veterans may never be determined given the limitations of the available data. To not acknowledge the uncertainty of what we know and the real possibility of not being able to identify a cause of the veterans' illnesses would be a disservice to medical science and more importantly to the men and women who served so courageously in this battleground.<sup>88(p259-60)</sup>

### *Comparison with Other Military Groups*

128. All modern wars have been associated with medically unexplained symptoms or syndromes<sup>118</sup> in returning military personnel deployed to war zones. For instance, a systematic comparison of UK pension files from previous wars (the Boer War, World War I, and World War II) with clinical files from the Gulf War revealed that 'chronic multisymptom illness' is similar to many post conflict syndromes. During the Boer War, soldiers complained primarily of fatigue, rheumatic pains, weakness, shortness of breath, rapid heart rate, headache, and dizziness.<sup>118</sup> In World War I and II, primary symptom complaints were chest pain, breathlessness, dizziness, and fatigue and to a lesser extent headache and anxiety.<sup>119</sup>
129. A number of researchers have examined the symptoms of Gulf War veterans compared to other military cohorts, and many have concluded there is no unique illness/syndrome.<sup>24, 100, 120-122</sup> In 1999, Ismail et al<sup>120</sup> reported on a population-based cross-sectional standardised survey (of 50 physical symptoms) of 12 592 men in three UK military cohorts; Gulf War veterans; Bosnia veterans; and non-deployed Gulf War veterans (called the 'era cohort'). Nearly all symptoms were reported more frequently in the Gulf War cohort. Using exploratory factor analysis to identify underlying factors and describe the grouping of symptoms reported in the Gulf War cohort, three factors together accounted for about 20% of the common variance. These factors were mood, respiratory system, and peripheral nervous system

symptoms. In the confirmatory factor analysis, based on the Haley case definition, the factor structure identified in the Gulf War cohort fitted reasonably well in the Bosnia and era cohorts. The authors concluded the findings do not support a unique Gulf War syndrome.

130. In 1999, Unwin et al<sup>24</sup> reported on the same study sample as that of Ismail et al<sup>120</sup> above. They reported that in the UK Gulf War veterans, Bosnia veterans, and non-deployed 'era cohort', respectively, 61.9%, 36.8%, and 36.4% met the CDC criteria for 'chronic multisymptom illness', which fell to 25.3%, 11.8%, and 12.2% for those with severe symptoms. The response rates were 70%, 62% and 63% respectively. 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 since associations of ill health with adverse events and exposures were found in all cohorts, they might not be unique and causally implicated in Gulf-War-related illness. Similarly, in a cross-sectional study of women in the Gulf compared to Bosnia veterans, in 2002 Unwin et al<sup>86</sup> reported that women deployed to the Gulf had similar rates of ill health as their male counterparts (response rate 65%).

131. In 2002, Everitt et al<sup>100</sup> reported on a random sample of 500 veterans from each of the three UK military cohorts described above; Gulf War veterans; Bosnia veterans (involved in the peacekeeping mission); and non-deployed veterans ('era cohort'). Computationally it was not feasible to apply the clustering analysis to all 8195 responding veterans, so 500 from each group were randomly selected. The authors identified five symptom clusters using factor analysis. Cluster 1 (by far the largest cluster) consisted of mildly symptomatic individuals who had low scores for all symptom groups. Cluster 2 had veterans with highest symptom scores for musculoskeletal symptoms and high scores for psychiatric symptoms and was more common in Gulf War veterans. Cluster 3 had high scores for neuropsychiatric symptoms and was more common in Gulf War veterans. Cluster 4 had elevated scores for musculoskeletal symptoms only and did not differ between cohorts. Cluster 5 was very small, of only 26 individuals, and was distinguishable from the other clusters in having high scores in all symptom groups, especially psychiatric and musculoskeletal, and 85% of these men were Gulf War veterans. The authors concluded that the findings do not support the existence of a unique syndrome affecting a subgroup of Gulf veterans but emphasised the excess of non-specific self-reported symptoms, particularly neuropsychiatric and musculoskeletal, in the Gulf War veterans group.

132. In 2003, Hotopf et al<sup>121</sup> reported the health effects in UK veterans of Bosnia peacekeeping and a comparison group of non-deployed military personnel (era veterans). Similar response rates were attained in Bosnia (63%) and the era veterans (62%). A proportion of the Bosnia group had served in the Gulf War and were found to have considerably worse health outcomes than the remaining Bosnia group or the era group. The Bosnia group who had not served in the Gulf War had broadly similar health outcomes to the era group. The main differences were that the Bosnia-only group consumed more alcohol and reported more fatigue, hay fever, weight gain, irritability, avoidance, and night sweats. Apart from heavy alcohol consumption, the magnitude of these differences was small. The Bosnia-only group had slightly better physical functioning than the era group, and there were two other symptoms and one ailment, which were less common in the Bosnia-only group than in the era group.

133. In 2006, Hotopf et al<sup>122</sup> reported results of a cohort study of 4722 UK 2003 Iraq War veterans (response rate 62%) and 5550 non-deployed veterans (response rate 56%). There was a modest increase in the number of individuals with multiple physical symptoms (OR 1.33, 95% CI 1.15-1.54). For regular UK military personnel, there were no specific health effects of deployment to the 2003 Iraq War. Rates of psychiatric symptoms were not any higher than that of the rest of the UK armed forces. Deployment did not have any effect on the health of regulars, apart from the slight increase in physical symptoms noted above.

134. In 2006, Horn et al<sup>123</sup> reported on the self-reported health status of UK service personnel after the 1990 – 1991 Gulf and 2003 Iraq Wars. Response rate was 61%. There were only slight increases in common symptoms in the 2003 Iraq War group, and no pattern suggestive of a new syndrome was present. Personnel deployed to the Gulf War were more likely (OR 2.00, 95% CI 1.70-2.35) than those not deployed to report their health as fair or poor; no such effect was found for the Iraq War (OR 0.94, 95% CI 0.82-1.09).

### *Animal Studies*

135. The Council noted that the Applicant had referred to a number of 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.

### *Summary*

136. The possibility that such symptoms and health outcomes represent a unique “Gulf War syndrome” has been extensively investigated. Gulf war veterans report a wide variety of symptoms more commonly than other veterans do. However, similar symptoms occur commonly in non-deployed veterans, in other groups and in the general population and the types and patterns of symptoms are similar in all groups.

## **COUNCIL’S EVALUATION OF THE SOUND MEDICAL-SCIENTIFIC EVIDENCE**

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

138. 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 articles, as it considered appropriate.

139. 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 articles.

140. The Council reviewed all the available SMSE, and it gave particular focus in its evaluation to those papers that provided research data from which the Council could draw conclusions about Gulf War syndrome.

## **COUNCIL’S CONCLUSIONS ON THE RELEVANT SOUND MEDICAL-SCIENTIFIC EVIDENCE**

141. In reaching a decision about the **existence or otherwise of a particular kind of disease, injury or death**, the Council must consider and evaluate all of the SMSE and ultimately conclude on the balance of probabilities whether or not the identified condition (in this case Gulf War syndrome) meets the definition of an injury or disease as defined in the Act.

142. 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.

### **THE COUNCIL'S CONCLUSIONS ON WHETHER THERE SHOULD BE STATEMENTS OF PRINCIPLES GULF WAR SYNDROME OR ILLNESS**

143. The Council concluded, **on the balance of probabilities**, that the evidence does not support that there is a disease or injury as defined in the Act described as Gulf War syndrome.

144. The Council noted that veterans of the 1990 – 1991 Gulf War are one of the most widely studied military groups in history, and after 26 years following the war, new information continues to be published. However, even though new literature on the health of Gulf War veterans is being added, the Council considered that no distinct disease or set of symptoms has been clearly identified.

145. The Council considered that the absence of established agreement on terminology to collectively define the unexplained health symptoms reported by Gulf War veterans, and the interchangeable use of terms, has made the evaluation and the comparison of the SMSE difficult. The Council noted the recommendation by the IOM in the 2014 report<sup>11</sup> on the use of the term 'Gulf War illness' rather than 'chronic multisymptom illness' but considered that this recommendation is not consistent with the weight of the SMSE and previous reports by the IOM.<sup>87, 88</sup> Nor is it internally consistent with the findings detailed in the 2014 IOM report that there was no consensus case definition for Gulf War syndrome and that there was no unique syndrome associated with Gulf War deployment.

146. The Council noted that Australian Gulf War veterans and their counterparts from the US, Canada, UK and Denmark consistently report higher levels of symptoms than non-deployed military personnel and people deployed to some other areas of operation.<sup>8, 11, 12, 17, 20, 43, 47, 69, 80-82, 87, 97, 99-101, 103, 105</sup> However, in contrast to the consistently increased reporting of symptoms, there have been no consistent findings with respect to a specific pattern of symptoms, physical signs on medical examination, or abnormalities detected on laboratory investigation.

147. The Council noted that while a number of different working case definitions have been developed<sup>10, 17, 74-78</sup> they have not been broadly reproducible across different Gulf War veteran groups and thus no consensus case definition has been established. In 2014 the IOM<sup>11</sup> committee recommended the use of two published case definitions of 'Gulf War illness'<sup>10, 17</sup> which the authors considered best capture the array of symptoms most commonly identified

by the evidence, best reflect the symptom complexes demonstrated by the Gulf War veterans, and provide a framework for further research. However, the IOM could not recommend one case definition over the other, and recommended these two case definitions “with some reticence.” A consensus case definition of ‘Gulf War illness’ has not been agreed upon by other health organisations.

148. In the 2014 Chronic Multisymptom Illness in Gulf War veterans: Case definitions Re-examined report, the IOM committee stated:

Although chronic multisymptom illness is descriptive of the heterogeneity of the symptoms, it is not specific to the population and its unique experience. Thus, to capture the population of interest and the symptoms, a preferred term is Gulf War illness. Illnesses are sometimes named after the geographic area or the group in which they were first identified without meaning to convey a sole etiology (for example, the 1918 influenza pandemic referred to as the Spanish flu, the 1968 and 1969 influenza outbreaks referred to as the Hong Kong flu, and pneumonia in legionnaires referred to as Legionnaire’s disease). The committee’s recommendation reflects both the geographic area and the unique experiences of this group of veterans. Gulf War illness has been used by many researchers to identify the array of symptoms expressed by Gulf War veterans. Its consistent use in the literature might reduce confusion.<sup>11(p99)</sup>

149. The Council noted the limitations with the available Gulf War syndrome case definitions, in that they were developed in different study populations (such as US Naval Seabees, US Air Force, Kansas veterans) and differ in their sensitivity and specificity, with no one case definition addressing all areas of symptom onset, duration, severity, frequency of symptoms, and exclusionary criteria.<sup>11</sup> Additionally, the use of different case definitions by different studies makes it difficult to compare results, and depending on the case definition used, the prevalence estimates vary greatly.

150. The Council noted many of the symptoms reported by Gulf War veterans overlap with other health conditions such as fibromyalgia, chronic fatigue syndrome, and various psychiatric disorders including PTSD, suicide, anxiety, depression and substance abuse.<sup>124</sup> However, the current available Gulf War Syndrome case definitions do not clearly differentiate Gulf War syndrome from these chronic conditions and Gulf War veterans’ chronic symptoms.

151. The Council found that there is limited information available to quantify the symptoms (such as onset, duration, severity, and frequency) and exposures (such as duration, intensity, and

frequency) reported by Gulf War veterans during their service. Therefore, most of the studies rely on self-reported symptom data, mostly from postal surveys. These have inherent problems of recall bias, as symptoms and exposures were often self-reported by Gulf War veterans many years after the Gulf War. Self-reporting symptoms also potentially introduces reporting bias, which can occur if Gulf War veterans over-report particular symptoms compared to non-deployed veterans, leading to an overestimation of the prevalence of symptoms or diagnoses in the deployed population.

152. The Council noted that many of the available studies have used the statistical technique of factor analysis to determine whether Gulf War veterans' symptoms might constitute a new syndrome, and thus to develop a case definition. Factor analysis is a statistical method for conducting structural analyses of datasets to identify the inter-relationships between certain variables among a large set of observed variables (i.e. a large number of varied symptoms). Then, through data reduction, a smaller set of variables are grouped into factors that have common characteristics (i.e. symptom groups).<sup>11</sup> The Council noted that there are limitations in the use of factor analysis particularly in the context of the development of a case definition for Gulf War veterans. Different studies have identified different numbers of factors and assigned different names to common groups of symptoms.<sup>15, 17, 125</sup> There is also a lack of consistency in these studies, because of differences in methodology, collection and quality of data, and random variation.<sup>11</sup> The methodology used can differ between studies as the determination of retained factors can be subjective, which can lead to non-reproducible combinations of factors, limiting both the generalisability and external validity of the data. The data is most often self-reported, with Gulf War veterans reporting symptoms and diagnoses, based on a cross-sectional examination of these symptoms or diagnoses. Therefore, the quality and accuracy of the data used to formulate the case definition is often subjected to recall and response bias, limiting overall validity. While factor analyses can reduce a large and varied amount of symptoms into smaller groupings, there is often a reasonable amount of overlap with other conditions such as chronic fatigue syndrome and fibromyalgia.

153. The Council also noted the poor response rates within studies, which can have considerable potential for selection bias. Response rates were reported to be as low as 41% in one study,<sup>74</sup> and in most studies were lower in non-deployed cohorts than in Gulf War veterans.<sup>116</sup>

154. The Council, based on its evaluation of the studies discussed above, has noted that while there is consensus that Gulf War veterans are more likely to report more symptoms than their non-deployed peers are, there is no consensus in the medical scientific literature that these comprise an illness or syndrome unique to veterans of the Gulf War.

155. The Council acknowledges the concerns of Gulf War veterans, particularly where they are suffering from unexplained health symptoms, and is empathetic to their concerns. The Council noted that the RMA determined SoP for chronic multisymptom illness in 2014.<sup>95</sup> These SoPs used the definition of 'chronic multisymptom illness' as defined by the CDC<sup>17</sup> but restricted the SoP to the severe form of 'chronic multisymptom illness' (as per the CDC definition). Two further stipulations were also added; 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. These SoPs are not specific to any geographical area, and are available to veterans of the Gulf War, as well as to veterans of other conflicts, and to eligible persons more generally. Factors in the chronic multisymptom illness SoPs have been the subject of a separate review by the SMRC.

156. Having decided that Gulf War syndrome is not a particular kind of disease or illness, the Council has no power under the Act to determine a SoP.

### **COUNCIL'S ANALYSIS OF THE NEW INFORMATION FOR GULF WAR SYNDROME**

157. As mentioned above, in conducting a review, the Council is 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.

158. The Council has neither the capacity nor the jurisdiction to perform an investigative function, including undertaking a comprehensive literature search.

159. 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.



160. 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 condition satisfying the definition of an injury or disease and, if so, the contended factor; and could potentially satisfy the reasonable hypothesis and/or balance of probabilities tests (as appropriate; see paragraph [171] below for the relevant associations).

#### *New Information Identified By the Applicant*

161. The Applicant referred a number of new papers to the Council. Of those, the Applicant referred to a new paper concerning the definition of disease and Gulf War veterans.

- Kuehn BM. Gulf War Illness defined. JAMA. 2014;311(16):1603.

162. In respect to this new paper the Council noted:

- This was an opinion piece, by Kuehn<sup>126</sup> that restates the IOM's 2014 report recommendation that the Department of Defense and others use the term Gulf War illness moving forward and that researchers and clinicians use case definitions created by the US CDC<sup>17</sup> or Steele's Kansas definition<sup>10</sup>. The Council noted the recommendation by the IOM that the US VA use the term 'Gulf War illness' to describe the collection of symptoms in this group. Despite a large volume of research conducted in this group of veterans, a unique disease, specific for the veterans of the Gulf War has not been established.

163. The Council noted that the Applicant also referred to a number of new animal studies<sup>54-57</sup> however, the Council has made comment on its position on the use of animal studies at [135].

#### *New Information Identified By the Council*

164. The Council did not undertake a comprehensive analysis of new information; therefore, no new papers were identified.

**COUNCIL'S CONCLUSIONS ON WHETHER IT SHOULD MAKE ANY RECOMMENDATIONS TO THE RMA ON THE BASIS OF THE NEW INFORMATION**

165. The Council acknowledges that substantial research has focussed on this group of veterans.

However, the Council considered that the new papers referred to it do not in its view warrant the Council making any recommendations to the RMA for a new investigation.

**DECISION**

166. The Council made the declarations summarised in [1] above.

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