The IOM Gulf War and Health Series

Presentation to the Research Advisory Committee on Gulf War Veterans' Illnesses

April 20, 2015

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The Institute of Medicine asks and answers the nation's most pressing questions about health and health care.

•The IOM is an independent, nonprofit organization that works outside of government to provide unbiased and authoritative advice to decision makers and the public.

•Established in 1970, the IOM is the health arm of the National Academy of Sciences, which was chartered under President Abraham Lincoln in 1863.

The IOM serves as adviser to the nation to improve health.

- Unbiased, authoritative advice
- Evidence-based recommendations
- Committees composed of experts in the fields of interest
- Committee members serve pro bono
- Neutral venue for open dialogue and discussion
- Honorific organization (not all committee members are IOM members)

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Origin of the Gulf War and Health Series

•Request from the Department of Veterans Affairs, and

•Public laws:

- Veterans Programs Enhancement Act of 1998 (Public Law 105-368) (Sen. Rockefeller) passed November 11, 1998 (does not have "presumption of exposure" clause)
- Persian Gulf War Veterans Act of 1998, Public Law 104-277) (Sen. Byrd) passed October 21, 1998 ("presumption of exposure" clause)
- Veterans' Benefits Act of 2010 (Public Law 111-275) passed October 13, 2010
- 33 agents identified in original congressional legislation

•VA or IOM may recommend additional studies (numerous additional studies have been conducted under this legislation)

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Agents in the Gulf War Legislation

(A) The following organophosphorous pesticides:
- (i) Chlorpyrifos.
- (ii) Diazinon.
- (iii) Dichlorvos.
- (iv) Malathion.

(B) The following carbamate pesticides:
- (i) Proxpur.
- (ii) Carbaryl.
- (iii) Methomyl.

(C) The carbamate pyridostigmine bromide used as nerve agent prophylaxis.

(D) The following chlorinated hydrocarbons and other pesticides and repellents:
- (i) Lindane.
- (ii) Pyrethrins.
- (iii) Permethrins.
- (iv) Rodenticides (bait).
- v) Repellent (DEET).

(E) The following low-level nerve agents and precursor compounds at exposure levels below those which produce immediately apparent incapacitating symptoms:
- (i) Sarin.
- (ii) Tabun.

(F) The following synthetic chemical compounds:
- (i) Mustard agents.
- (ii) Volatile organic compounds.
- (iii) Hydrazine.
- (iv) Red fuming nitric acid.
- (v) Solvents.

(G) The following sources of radiation:
- (i) Depleted uranium.
- (ii) Microwave radiation.
- (iii) Radio frequency radiation.

(H) The following environmental particulates and pollutants:
- (i) Hydrogen sulfide.
- (ii) Oil fire by products.
- (iii) Diesel heater fumes.
- (iv) Sand micro-particles.

(I) Diseases endemic to the region such as:
- (i) Leishmaniasis.
- (ii) Sandfly fever.
- (iii) Pathogenic escherichia coli.
- (iv) Shigellosis.

(J) Time compressed administration of multiple live, "attenuated", and toxoid vaccines.

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Study Charge as a Result of Legislation

IOM committees have determined the association between exposure to the agents listed in the legislation and long-term adverse health effects in more than 10 volumes:

1. (2000): pyridostigmine bromide, sarin, depleted uranium, and vaccines
2. (2002): 12 insecticides and one insect repellent and 53 solvents
3. 2004): hydrazines, nitric acid, fuels and combustion products
4. (2006): all health effects in Gulf War veterans vs non-deployed counterparts (no conclusions on level of association)
5. (2006): infectious diseases pertinent to Gulf War Veterans
6. (2007): deployment-related stress
7. (2009): traumatic brain injury
8. (2010): update of Volume 4
9. (2014): blast injuries
10. (2016): update of Volumes 4 and 8

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Additional study requests from the legislation

- To determine long-term adverse health effects associated with
  - Sarin Update (2004) reviewed new literature on sarin and organophosphate pesticides and long-term health effects
  - Depleted Uranium Update (2008) reviewed long-term health outcomes associated with depleted uranium (update of Volume 1 findings)
- Amyotrophic Lateral Sclerosis (ALS) in Veterans (2006)
- Treatment of Chronic Multisymptom Illness (GWI) (2013)
- Case Definition of Chronic Multisymptom Illness (GWI) (2014)

IOM committees were NOT asked

- To determine whether a unique Gulf War syndrome exists, or to make judgments regarding the veterans' levels of exposure to putative agents
- To focus on broader issues, such as the potential costs of compensation for veterans or policy regarding such compensation

The IOM Study Process

- Prospective members are suggested by individuals knowledgeable in the fields for which nominees are sought including IOM members, Board members, general public
- Governmental agencies that sponsor projects are not permitted to select members, however, sponsors and other organizations can suggest nominees
- All nominations are approved by chair of the NRC
- Members are chosen on the basis of knowledge and experience
- Before appointments are finalized:
  - names, affiliations, and short biographies posted for public comment on the National Academies' website for 20 days
  - vetted for potential or perceived conflicts of interest and biases
- Every attempt is made to have a balanced committee with a commitment to review the evidence with an open mind

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The Study Process – Committee Deliberations

- Meetings can include 'information gathering sessions' during which the sponsor, other experts, and the public can present to the committee
- Portions of meetings at which individuals other than the committee members and IOM staff are present are open to the public
- All other committee deliberations occur in closed session
- IOM posts upcoming meeting dates and agendas, as well as a closed session summary, on the Academies' website
- IOM also posts materials received by the committee from external sources, including the sponsor and public to each committee's public access file. These materials may be viewed by anyone upon request
- IOM strives to have consensus reports; dissenting opinions may occur and can be resolved or acknowledged in the report

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The Role of the Sponsor

- Attend open, information gathering sessions
- Can provide suggestions for nominees for the committee (they will be considered along with suggestions from other sources)
- Addresses the committee during an open session, typically at the first meeting, to articulate their perspective on the charge to the committee
- Provide information, through the IOM staff, to the committee as requested by the committee; no direct contact with committee members

The Study Process – Report Review and Release

- Prior to release, the report is reviewed by individuals independent of the institution, who are not involved in authoring the report and whose names are not revealed to the committee during review
- Reviewers are selected by the major unit responsible for the project, in consultation with the National Academies Report Review Committee
- Review is overseen by a review monitor and/or coordinator
- Report may not be released to sponsor or the public until chair of the Report Review Committee (or designee) signifies that review process has been satisfactorily completed
- Once finalized, typically briefings and embargoed copies of report are provided to sponsor and Congress just prior to public release of the report. Only factual errors may be corrected, no other changes to the report may be made

Committee's Approach

- Review all peer-reviewed published literature (occasionally gray literature as well)
- No preconceived ideas of what outcomes may be found
- Human epidemiologic studies have more weight than animal studies
- All studies reviewed by entire committee to reach consensus on whether a study is key/supporting
- Animal studies alone are not sufficient to determine strength of association (inasmuch as there is ample literature on health effects from occupational exposures)

Committee's Approach (cont'd)

- Most Gulf War studies compare deployed with nondeployed or deployed-elsewhere veterans
- Other studies such as brain imaging and studies on biomarkers such as enzymes and neurotransmitters, are informative and assessed, but are often difficult to link to clinical outcomes, e.g., diagnosis or treatment
- For some exposures, it may be necessary and appropriate to consider surrogate populations

Categories of Association Used in Determining the Strength of the Evidence

Sufficient Evidence of a Causal Relationship*. Evidence is sufficient to conclude that a causal relationship exists between the exposure to a specific agent and a health outcome in humans. The evidence fulfills the criteria for sufficient evidence of an association (below) and satisfies several of the criteria used to assess causality: strength of association, dose–response relationship, consistency of association, temporal relationship, specificity of association, and biological plausibility.*

Sufficient Evidence of an Association*.* Evidence is sufficient to conclude that there is a positive association; that is, a positive association has been observed between an exposure to a specific agent and a health outcome in human studies in which chance, bias, and confounding could be ruled out with reasonable confidence.

Limited/Suggestive Evidence of an Association*.* Evidence is suggestive of an association between exposure to a specific agent and a health outcome in humans, but is limited because chance, bias, and confounding could not be ruled out with confidence.

Inadequate/Insufficient Evidence to Determine Whether an Association Does or Does Not Exist. Evidence is of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association between an exposure to a specific agent and a health outcome in humans.

Limited/Suggestive Evidence of No Association*.* Evidence from several adequate studies, covering the full range of levels of exposure that humans are known to encounter, that are mutually consistent in not showing a positive association between exposure to a specific agent and a health outcome at any level of exposure. A conclusion of no association is inevitably limited to the conditions, levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.

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Findings from Gulf War Reports
Volumes 1, 2, 3, 6, 8, and 9

Sufficient evidence of a causal relationship

- Benzene and acute leukemia and aplastic anemia
- Sarin and a dose-dependent acute cholinergic syndrome
- Blast injuries and penetrating eye injuries and some long-term effects on a genitourinary organ
- Deployment to the Gulf War and PTSD

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Findings from Gulf War Reports (cont'd)

Sufficient evidence of an association

- Benzene and adult leukemia
- Solvents and acute leukemia
- Propylene glycol and contact dermatitis
- PB and transient acute cholinergic effects
- Anthrax vaccination and transient acute local and systemic effects
- Botulinum toxoid vaccination and transient acute local and systemic effects
- Combustion products and lung cancer
- Deployment related stress and psychiatric disorders (PTSD, other anxiety disorders, depressive disorders), alcohol abuse, accidental death, suicide, marital and family conflict
- Blast and PTSD, endocrine dysfunction, postconcussive symptoms and persistent headache, permanent neurologic disability, and long-term dermal effects
- Deployment to the Gulf War and other psychiatric disorders (including anxiety disorder depression, and substance abuse), functional gastrointestinal disorders, multisymptom illness, and chronic fatigue syndrome

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Recommendations for Future Research

- Continuing need for well-designed follow-up studies of robust GW cohorts to track mortality; cancer (particularly brain cancer); neurologic and psychiatric outcomes, such as ALS and multiple sclerosis conditions; and other health conditions that occur later in life such as cardiovascular disease, other cancers, and neurodegenerative diseases
- Further study of the functional gastrointestinal disorders
- Large studies to identify genetic variants and rare environmental events related to outcomes

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Further Research Recommendations

- Additional investigations based solely on self reports are unlikely to provide more information on GW illness
- It is difficult to reconstruct exposures from 25 years ago but …
- Rigorous studies are still needed to identify biomarkers of GW illness using genetics, molecular diagnostics, and imaging. These may help with diagnosis and treatment of the illness, even if they are unlikely to identify the cause

Questions?