National Academies of Science, Engineering and Medicine (NASEM) Gulf War and Health, Volume 11, Generational Effects of Serving in the Gulf War

Presented by: Dr. Karen Block on behalf of the Intergenerational Effects Of Military Exposures Working Group (IEMEWG) Co-Chaired by Dr. Block, Dr. Victoria Davey and Dr. Marc A. Williams
Presented to: Research Advisory Committee on Gulf War Veterans' Illnesses
Date: February 7, 2023

Agenda

1. Background
2. National Academy of Science, Engineering and Medicine (NASEM) Findings and Recommendations
3. Intergenerational Effects of Military Exposures Work Group (IEMEWG)
4. Considerations and Challenges of Implementing a Comprehensive Health Monitoring Research Program (HRP)

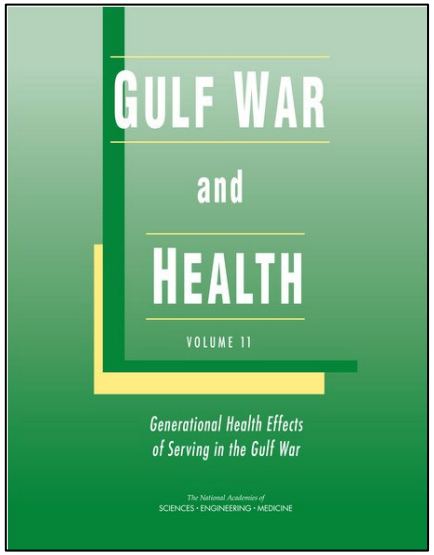
Background

PUBLIC LAW (PL) 114-315

- In 2016, PL 114-315 mandated that the Department of Veterans Affairs (VA) contract with the National Academy of Medicine (NAM) to assess research relating to descendants of individuals with toxic exposures.
- The NASEM report, in *Gulf War and Health, Vol.11, Generational Effects of Serving in the Gulf War*, was released in November 2018.

Generational Health Effects of Serving in the Gulf War

KENNETH S. RAMOS (Chair), Associate Vice President for Precision Health Sciences, Professor of Medicine and Director, Center for Applied Genetics and Genomic Medicine, University of Arizona Health Sciences.



Gulf War and Health Vol. 11: Bottom Line Up Front

Findings and Recommendation

NAM found 27 ‘chemicals of interest’ associated with military service that could induce reproductive, birth or developmental health effects, but NAM did not find any evidence that these specific exposures were linked to health effects in the Gulf War and OIF/OEF military Service member populations.

NASEM recommended that VA establish a comprehensive *Health Monitoring and Research Program (HMRP).*

NAM Committee

The NASEM committee organized the toxicants of concern into four groups and reviewed the evidence for an association between Gulf War deployment exposures and reproductive effects in men or women, adverse pregnancy outcomes, or developmental effects

1. Deployment-related exposures
    - Deployment itself
    - Vaccines
    - Chemical warfare agents
    - Infectious diseases
    - Depleted uranium
    - Hexavalent chromium
    - Pyridostigmine bromide
2. Pesticides
3. Combustion products and fuels
4. Solvents

Summary – Sufficient Evidence of a Causal Relationship

Definition:

Evidence is sufficient to conclude that a causal relationship exists between being exposed to a toxicant and a reproductive or developmental effect in humans. The evidence fulfills the criteria for sufficient evidence of a causal association in which chance, bias, and confounding can be ruled out with reasonable confidence.

Findings:

None

Summary - Sufficient Evidence of an Association

Definition:
Evidence suggests an association, in that a positive association has been observed between an exposure and a reproductive or developmental effect in humans; however, there is some doubt as to the influence of chance, bias, and confounding.

Findings:

- Leishmaniasis infection during pregnancy, adverse pregnancy outcomes
- Hexavalent chromium, male reproductive effects
- Prenatal exposure to hexavalent chromium and developmental effects
- Prenatal exposure, organophosphate pesticides and neurodevelopmental effects
- Carbamate pesticides, male reproductive effects
- Prenatal exposure to particulate matter and adverse pregnancy outcomes – low birth weight/preterm births

Summary - Limited or Suggestive Evidence of an Association (1 of 2)

Definition:

Some evidence of an association between exposure and a reproductive or developmental effect in humans exists, but this is limited by the presence of substantial doubt regarding chance, bias, and confounding.

Findings:

- Sulfur mustard and male reproductive effects
- Hexavalent chromium and adverse pregnancy outcomes
- Organophosphate pesticides and male reproductive effects
- Pyrethroid pesticides and male reproductive effects
- Lindane and female reproductive effects
- Prenatal exposure to pyrethroid pesticides and developmental effects
- Prenatal PM2.5 exposure, pregnancy-induced hypertensive disorders
- Prenatal PM2.5 – childhood respiratory, neurodevelopmental effects

Summary - Limited or Suggestive Evidence of an Association (2 of 2)

Findings (continued from previous slide):

- Polycyclic aromatic hydrocarbons and male reproductive effects
- Prenatal exposure to polycyclic aromatic hydrocarbons and adverse birth outcomes – low birth weight and preterm birth, or developmental effects – birth defects, childhood cancer, neurodevelopmental and respiratory effects
- Benzene and male reproductive effects
- Prenatal exposure to trichloroethylene (TCE) - developmental effects
- Prenatal exposure to perchloroethylene (PCE) - developmental effects
- TCE – male reproductive effects, adverse pregnancy outcomes
- Glycols and glycol ethers and male reproductive effects
- Prenatal exposure to glycols or glycol ethers and birth defects

Summary - Inadequate or Insufficient Evidence to Determine Whether an Association Exists (1 of 4)

Definition:

Available studies are of insufficient quantity, quality, validity, consistency, or statistical power to permit a conclusion on the presence or absence of an association between an exposure and a reproductive/developmental effect.

Findings:

- Deployment and reproductive/developmental effects
- Sarin/cyclosarin and reproductive/developmental effects
- Sulfur mustard and female reproductive effects, adverse pregnancy outcomes, or developmental effects
- Leishmaniasis and reproductive/developmental effects
- Anthrax vaccination and reproductive/developmental effects
- Depleted uranium and reproductive/developmental effects
- Prydostigmine bromide and reproductive/developmental effects
- Hexavalent chromium and female reproductive effects

Summary - Inadequate or Insufficient Evidence to Determine Whether an Association Exists (2 of 4)

Findings (continued from previous slide):

- Organophosphate pesticides and female reproductive effects or adverse pregnancy outcomes
- Prenatal exposure organophosphate pesticides and other developmental effects (not neurodevelopmental effects)
- Carbamate pesticides, female reproductive/adverse pregnancy effects
- Prenatal exposure to carbamates and developmental effects
- Pyrethroid pesticides – female reproductive, adverse pregnancy effects
- Lindane and reproductive or developmental effects
- DEET and male/female reproductive/developmental effects

Summary - Inadequate or Insufficient Evidence to Determine Whether an Association Exists (3 of 4)

Findings (continued from previous slide):

- PM2.5 and male/female reproductive effectsPrenatal exposure to PM2.5 and other developmental effects (not respiratory and neurodevelopmental effects)
- Polycyclic aromatic hydrocarbons and female reproductive effects
- Prenatal polycyclic aromatic hydrocarbons exposure and other developmental effects (not birth defects, childhood cancer, neuro-developmental effects and respiratory outcomes in childhood)
- Polychlorinated dibenzodioxins and polychlorinated dibenzofurans and reproductive/developmental effects
- Diesel exhaust and reproductive/developmental effects
- Fuels and reproductive/developmental effects
- Benzene and female reproductive or adverse pregnancy outcomes

Summary - Inadequate or Insufficient Evidence to Determine Whether an Association Exists (4 of 4)

Findings (continued from previous slide):

- Prenatal benzene exposure and other childhood developmental effects (not childhood leukemia)
- Toluene and reproductive/developmental effects
- Xylenes and reproductive/developmental effects
- Trichloroethylene and female reproductive effects
- PCE and male/female reproductive or adverse pregnancy outcomes
- Glycols/glycol ethers – female reproductive/adverse pregnancy effects
- Prenatal glycol/glycol ether exposure and other developmental effects (not birth defects)

Interim Summary – Findings and Conclusions

- No toxicant had sufficient evidence of a causal association between exposure and reproductive or developmental effects.
- Nor did any toxicant have limited/ suggestive evidence of no association between exposure and reproductive or developmental effects.
- Conclusions need to be interpreted within the broader context of both the Veterans' and their descendants' exposures over the courses of their lives.
- Exposures across the life course, beginning in utero, can have an impact on health, including that of future children. Those exposures, such as nutritional exposure and exposure to environmental toxicants, may interact with one another and be influenced by a person's genome and epigenome.
- Such changes are being studied, but at present there is not enough evidence to link any deployment exposures to epigenetic effects.

NASEM Recommended the establishment of a Health Monitoring Research Program (HMRP)

Objective: To help determine if Veterans' descendants are at risk for health effects resulting from Veterans' exposures during deployment, the committee proposed the creation of a health monitoring and research program (HMRP) with three arms:

1) monitor the reproductive, generational, and health outcomes of service members, veterans, their partners, and descendants (children, grandchildren, and great grandchildren) over their lifetime starting with entrance into the military;

2) collect exposure data, biospecimens, and health surveys; and

3) conduct epidemiological, basic, and clinical research.

VA Established an Intergenerational Effects of Military Exposures Working Group (IEMEWG)

Charge to IEMEWG:

Determine the Feasibility and Achievability of a Health Monitoring Research Program (HMRP) as outlined by NASEM

- The IEMEWG was co-chaired by VA and non-VA Subject Matter Experts.
- The IEMEWG included Federal partners with Subject Matter Expertise:
  - Department of Veterans Affairs (VA)
  - Department of Defense (DOD)
  - National Institutes of Health (NIH)
  - Centers for Disease Control and Prevention (CDC)
  - Health Resources & Services Administration (HRSA)
- Input from Academia and Veterans were solicited.

Determine Feasibility and Scalability of an HMRP: IEMEWG - Deep Dive Approach

Group 1: Clinical/Epidemiology

- Longitudinal Studies (parents/children)
- Birth Registries
- Health Outcomes (parents/children)
- Clinical Services (Pediatricians)
- Questionnaire (timeline)
- **EPIDEMIOLOGY CORE / HUB**

Group 2: Research

- Toxicants (common vs rare)
- Complex Mixtures
- Toxicant Dosing experiments
- F0, F1, F2, F3 in vitro, in vivo
- Genetics/Epigenetics
- Biological Outcome Characterization
- Biomarker Library
- In vitro/new approach methodologies or NAMs (Alternative Testing Strategies)
- In vivo (rats/mice/other)
- Imaging? Quantitative Pathology Diagnosis
- **RESEARCH CORE / HUB**

Group 3: Administrative Infrastructure

- Databases, IT support, Computing Infrastructure
- Metadata
- Data Accessibility (FAIR principles)
- Data Management Plans (DMPs)
- Quality Management Plans (QMPs) for Coding Data/Biospecimens
- Biobanking/Biorepositories and Freezer Space
- Federal Agency Collaboration/Agreements
- ACADEMIC INSTITUTIONS
- ILER
- APHC Toxicological Studies in vitro / NAMs, in vivo / PBPK and IVIVE
- Cost Analysis – Budget Constraints/Feasibility
- Staffing – Succession and Training
- **ADMINISTRTATIVE CORE / HUB**

Considerations and Challenges of an HMRP - Implementation

Basic Considerations

- Define the scope and establish the goals.
- Implement pilot studies to determine:
  - Feasibility of data collection strategies
  - Establish links for appropriate data use
  - Determine response rates for veterans and future generations
  - Can also consider evaluating survey or other data collection tools
- Employ focus groups and other exploratory processes:
  - Will help identify specific exposures and health effects of concern
  - Could identify populations, datasets, and administrative logistics
- To maximize success, an HMRP should target Veteran groups and/or specific exposures.
- Consider a tiered approach – will permit scale-up from pilot studies, to larger multi-entity population-based cohort studies.

Considerations and Challenges of an HMRP - Implementation

Enrollment and Recruitment

- New recruits enrolled on entering DoD using an opt-out process:
  - Will establish health status including lifestyle data and environment
  - Will secure biospecimen collection (at baseline) pre-deployment
- Veterans entering the VA healthcare system easier to identify:
  - Modified strategies needed to follow veterans not entering the system
- Enroll partners as they enter the MHS/TRICARE system:
  - Recruitment of children begins with those born to an active-duty Service member and covered under TRICARE
  - Recruitment and follow-up of older children, esp. as adults presents additional feasibility and ethical concerns
- Long-term follow-up studies requires appropriate participant consent (e.g., NHANES provides exemplar models on the approach).

Considerations and Challenges of an HMRP - Implementation

Collection and Sources of Data

- An HMRP should collect data across three critical domains:
  - Biological samples/specimens – to include genetic, epigenetic, exposome data
  - Environmental signature – to include biological, chemical toxicant exposures
  - Behavioral/social determinants – to include lifestyle, socio-economic, life events
- Potential sources of data:
  - Electronic health records – DOD, VA, Others (e.g., Medicaid)
  - DOD individual longitudinal exposure record (ILER), environmental sampling studies
  - Periodic surveys – veterans, partners, decedents – lifestyle/other exposures
  - Biorepositories – DOD Serum Repository, state collections of infant dried blood spots (DBS)

Considerations and Challenges of an HMRP - Implementation

Specimen and Data Collection – Logistics and Novel Approaches

- Data collected from Service members upon entry to the Military, and then immediately pre-deployment and on post-deployment.
- Data collected directly from children - to document outcomes and provide assessment of risk factors through childhood at key milestones.
- Biospecimen collection (blood/serum, urine and semen) from recruited HMRP participants will require:
  - Specimen coding, data management plans, GLP procedures
  - Database networking, advanced statistical analyses (esp. DoD and VA electronic health records) – critical administrative need
  - Novel approaches needed to identify populations, and specific data needs
- To strengthen response rates - HMRP participation/retention will require:
  - Incentives
  - Reminders
  - Use of social media platforms, etc.

Considerations and Challenges of an HMRP - Implementation

Leveraging Existing Programs and Activities

- Ongoing Programs Leveraged
  - Million Veteran Program
  - Millennium Cohort Study
  - DOD Birth and Infant Health Registry
  - DOD Serum Repository
- Advantages of Leveraging
  - Cost Reductions
  - Expedited Data Collections and Analyses
  - Access Already Engaged (and Available) Study Populations
- Will require periodic evaluation of program goals and aligned activities
- Permits any modifications to optimize HMRP effectiveness and mission

Other Considerations of implementing the HMRP

FACT: Broad Scope. A HMRP, as outlined by NASEM would:

1) monitor the reproductive, generational, and health outcomes of service members, veterans, their partners, and descendants (children, grandchildren, and great grandchildren) over their lifetime starting with entrance into the military;
2) collect exposure data, biospecimens, and health surveys; and
3) conduct epidemiological, basic, and clinical research.

FACT: If the HMRP is determined to be feasible, additional requirements from PL 114-315 will be triggered, including:

1) creation of a VA Federal Advisory Committee that will oversee the research and
2) a prohibition against VA conducting the research.

Conclusion: The IEMEWG does not support creation of a comprehensive Health Monitoring Research Program

14 of the 15 IEMEWG members concluded that an HMRP is not feasible and provides a 6-point rationale for NOT supporting creation of an HMRP:

1) Insufficient scientific evidence that toxic exposure-induced generational effects have occurred in military service members who deployed to the Southeast and Southwest Asia theaters of operation.

2) Multiple short-and long-term barriers to achievability in epidemiological studies, clinical requirements, and research.

3) Feasibility and scalability concerns to meet administrative and infrastructure requirements exist.

4) Governance and ownership for the HMRP cannot be determined due to the inability of VA to be an entity of the research as outlined in Public Law (PL) 114-315.

5) Prior efforts have failed. Similar comprehensive implementation- and environmental health monitoring-based children's studies were deemed not feasible after $1.6 billion dollars had been invested.

6) Lack of a National Health Record and a National Birth Defect database from which to draw data.

Report of the
Intergenerational Effects of Military Exposures
Work Group

to the
Secretary of Veterans Affairs

In response to Public Law 114-315, sec. 632 (d)

Pages: 1-72

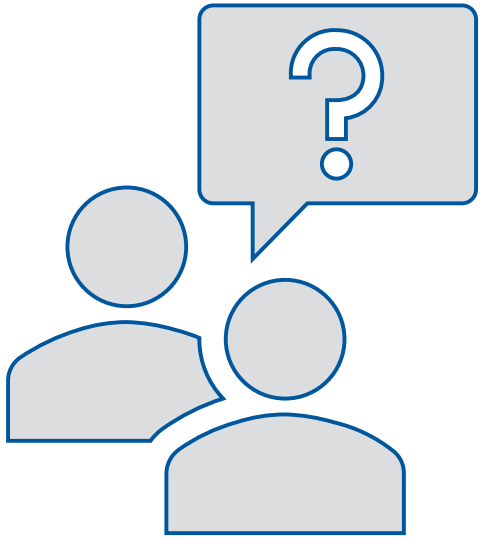
Secretary of Veterans Affairs

Certified to Congress, 2021

Public Law 114-315, section 632(d)

- After considerable investigation and discussion, I certify my understanding that further research as outlined in the NASEM report **is not feasible**.
- In reaching this reasoned judgment, I relied on the work undertaken by a fifteen-member working group that provided perspective from several Federal agencies as well as subject matter expertise on exposures, birth defects and men's and women's health.
- At the conclusion of its work, the group determined that the type of HMRP discussed in the NASEM report would ultimately fail.

Questions and Discussion



BACK UP SLIDE: Other Notable Considerations Concluded by the IEMEWG

- **Note:** Evaluation of chemical and/or environmental factors that may result in an altered reproductive health or birth defect outcome in humans is challenging.

1) If exposures are limited to somatic cells and no mutations occur in the germline and/or germline stem cells, the mutations will not be passed to future generations. The same holds true with permanent epigenetic modifications in germline cells. Further research may be beneficial in this nascent field of study.

2) There are windows of vulnerability (finite critical periods) during which an exposure can affect generational health including exposure to: A) parental gametes, B) the fetus directly during fetal development while *in utero*, or C) the fetal gametes while *in utero* during development. These finite critical windows are rare, will be different for each scenario, and there are biological cellular protective factors that inhibit damaged cells to survive.

3) Determining causality with the above multiple factors is unlikely to yield useful results at this time.