

GULF WAR AND HEALTH, VOLUME 11:  
GENERATIONAL HEALTH EFFECTS OF  
SERVING IN THE GULF WAR

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# Committee on Gulf War and Health, Volume 11: Generational Health Effects of Serving in the Gulf War

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# Statement of Task

A NASEM committee will conduct a study to assess the current research available on possible generational health effects that may be the result of exposures experienced by Veterans of the 1990-1991 Gulf War and the Post-9/11 wars during their deployments. The committee will consider which toxicants are known to be associated with pathophysiological and reproductive, developmental, and teratogenic effects across the lifecourse in parents, offspring, and 2nd-generation offspring.

The committee will also assess areas requiring further scientific study on the descendants of Veterans with toxic exposures. Finally, the committee will further assess the scope and methodology required to conduct research on such descendants to identify current or possible health effects in the Veterans' descendants, including but not limited to:

- Cellular pathophysiology studies associated with the long-term generational health effects of the toxicants of concern including studies in laboratory animals and other models;
- Multigenerational effects of the toxicants of concern in various animal species;
- The feasibility of conducting a long-term epidemiologic study to assess the generational health effects of Veterans and the resources (technological, logistical) needed to support such research;
- Develop a framework for monitoring and studying generational health effects, including post-exposure assessments, initial screening of Veterans and their descendants, the frequency and duration of such screenings;
- Based upon an assessment of available laboratory technologies, establish a process for what is to be included in the screening including biomarkers and early symptoms;
- The number of Veterans and their descendants who should be part of such a study(ies); and
- The appropriate federal agency(ies) or other organization(s) or collaborative consortia that would be best suited to coordinate and/or conduct the research and screenings on an ongoing basis.

# Committee's Approach

- Held two public sessions to hear from VA, DoD, NIEHS, NTP, CDC, VSOs, individual veterans
- Divided statement of task into two efforts:
  1. Considered what reproductive, developmental, and generational effects were already associated with the Gulf War toxicants in the existing literature and what data and knowledge gaps needed to be addressed to understand those effects
  2. Developed approaches for studying and monitoring potential health problems related to veterans' deployments and their impact on their children and grandchildren
- Conducted extensive literature searches, >4,000 papers reviewed
- Searches included studies carried out in human populations and animal or cellular experimental models

# Committee's Approach

- Reviewed information summarized in prior GW&H reports as a starting point for literature review, particularly Volumes 1, 2, and 3
- Considered existing reviews of epidemiologic and toxicologic data published by authoritative bodies, including prior National Academies' committees, the U.S. EPA, and ATSDR
- Discussed the entire data set for each toxicant and health outcome in plenary session and reached consensus as to the category of association to be assigned using a weight of the evidence approach
- Followed the evaluation processes established by previous Gulf War and Health and other National Academies committees, including the categories of association used by those committees

# Sufficient Evidence of a Causal Relationship

- None

## Sufficient Evidence of an Association

- Leishmaniasis infection during pregnancy and adverse pregnancy outcomes
- Hexavalent chromium and reproductive effects in men
- Prenatal exposure to hexavalent chromium and developmental effects
- Prenatal exposure to organophosphate pesticides and neurodevelopmental effects
- Carbamate pesticides and reproductive effects in men
- Prenatal exposure to particulate matter (PM) and adverse pregnancy outcomes—low birth weight and preterm birth
- Prenatal exposure to benzene and childhood leukemia

# Limited/Suggestive Evidence of an Association

- Sulfur mustard and reproductive effects in men
- Hexavalent chromium and adverse pregnancy outcomes
- Organophosphate pesticides and reproductive effects in men
- Pyrethroid pesticides and reproductive effects in men
- Lindane and reproductive effects in women
- Prenatal exposure to pyrethroid pesticides and developmental effects
- Prenatal exposure to PM and pregnancy-associated hypertensive disorders; and PM and respiratory or neurodevelopmental effects in children
- Polycyclic aromatic hydrocarbons (PAHs) and reproductive effects in men
- Prenatal exposure to PAHs and adverse birth outcomes, birth defects, childhood cancer, neurodevelopmental effects and respiratory outcomes in childhood
- Benzene and reproductive effects in men
- TCE and reproductive effects in men, or adverse pregnancy outcomes
- Prenatal exposure to TCE or perchloroethylene and developmental effects
- Glycols and glycol ethers and reproductive effects in men
- Prenatal exposure to glycols or glycol ethers and birth defects

# Inadequate/Insufficient Evidence to Determine Whether an Association Exists

- Deployment and reproductive or developmental effects
- Sarin/cyclosarin and reproductive or developmental effects
- Sulfur mustard and reproductive effects in women, adverse pregnancy outcomes, or developmental effects
- Leishmaniasis and reproductive or developmental effects
- Anthrax vaccination and reproductive or developmental effects
- Depleted uranium and reproductive or developmental effects
- Pyridostigmine bromide and reproductive or developmental effects
- Hexavalent chromium and reproductive effects in women
- OP pesticides and reproductive effects in women, or adverse pregnancy outcomes
- Prenatal exposure to OP pesticides and other developmental effects (other than neurodevelopmental effects)
- Carbamate pesticides and reproductive effects in women, or adverse pregnancy outcomes
- Prenatal exposure to carbamates and developmental effects
- Pyrethroid pesticides and reproductive effects in women, or adverse pregnancy outcomes



# Inadequate/Insufficient Evidence to Determine Whether an Association Exists

- Lindane and reproductive effect in men or developmental effects
- DEET and reproductive and developmental effects
- PM and reproductive effects in men and women
- Prenatal exposure to P and other developmental effects (other than respiratory and neurodevelopmental effects)
- PAHs and reproductive effects in women
- PAH exposure and other developmental effects (other than birth defects, childhood cancer, neurodevelopmental effects and respiratory outcomes in childhood)
- Polychlorinated dibenzodioxins and polychlorinated dibenzofurans and reproductive or developmental effects
- Exhaust and reproductive or developmental effects
- Fuels and reproductive or developmental effects

# Inadequate/Insufficient Evidence to Determine Whether an Association Exists

- Benzene and reproductive effects in women, or adverse pregnancy outcomes
- Prenatal exposure to benzene and other developmental effects in children (other than childhood leukemia)
- Toluene and reproductive or developmental effects
- Xylenes and reproductive or developmental effects
- Trichloroethylene and reproductive effects in women
- Perchloroethylene and reproductive effects in men and women, or adverse pregnancy outcomes
- Glycols and glycol ethers and reproductive effects in women, and adverse pregnancy outcomes
- Prenatal exposure to glycols or glycol ethers and any other developmental effects (other than birth defects)

## Limited/Suggestive Evidence of No Association

- None

# Animal Studies

For some toxicants, the animal data were robust, but the lack of human data precluded the committee from assigning a category of association that reflected a stronger level of association. These toxicants include:

- Depleted uranium and reproductive effects in males;
- Lindane and reproductive effects in males and developmental effects in offspring;
- Toluene and developmental effects in offspring;
- Xylenes and developmental effects in offspring;
- Trichloroethylene and reproductive effects in females; and
- Dioxins and reproductive effects in males and females.

There is some evidence of intergenerational effects in human and animal studies with prenatal exposures, but evidence of transgenerational effects is lacking in humans and sparse in animals.

# Health and Monitoring Research Program

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:

- Monitoring the health of veterans and their descendants over time;
- Epidemiologic studies to examine groups of veterans and their descendants for health outcomes of concern;
- Basic and translational research to address data and knowledge gaps.

# Framework for an HMRP (1)

- Define scope and establish program goals.
- Conduct pilot programs to determine the feasibility of collection strategies, establish linkages for appropriate use of data, assess response rates among veterans and their descendants, or evaluate surveys or other data collection tools.
- Use focus groups and other exploratory strategies to help identify specific exposures and health effects of concern, populations, datasets, and logistics.
- HMRP must be tailored to specific veteran groups and/or exposures in order to maximize opportunities for success.
- Use a tiered approach to scale up from pilot programs to large, multi-institution epidemiologic cohort studies.

# Framework for an HMRP (2)

- Enroll all new recruits as they enter DoD using an opt-out approach, to establish health status, including information on lifestyle and environment, as well as secure biological samples, prior to deployment.
- Veterans who enter the VA health care system will be easier to identify, but modified strategies will be needed to follow veterans who do not enter the system.
- Enroll partners at their enter the MHS/TRICARE system.
- Children recruitment may begin with those who are born to an active-duty service member and covered under TRICARE.
- Recruitment and follow-up of older children, particularly when they are adults poses additional feasibility and ethical challenges.
- Long-term follow-up studies will require appropriate participant consent. There are good models for such consenting, e.g., NHANES.

# Framework for an HMRP (3)

- Any HMRP should collect data in three key dimensions:
  - Biological samples to include a person's genome, epigenome, proteome, microbiome, physiology, metabolome/exposome, and health status;
  - Environmental factors to include exposures to biological, physical, and chemical agents in air, water, and soil;
  - Personal and social factors to include occupations, lifestyle habits, education, life events, and neighborhood.
- Sources of such data include the following:
  - Electronic health records (EHRs) from DoD, VA and possibly other health care providers (e.g., Medicaid or private providers)
  - DoD individual longitudinal exposure record (ILER when available) and environmental sampling studies at deployment locations
  - Periodic surveys of veterans, partners, and descendants about lifestyle and other exposures
  - Biorepositories such as the DoD Serum Repository and state collections of infant blood spots

# Framework for an HMRP (4)

- Samples should be collected from service members upon entry into the military, prior to each deployment, and after each deployment.
- For veterans, periodic sample collections will depend on the goals of the HMRP.
- Data collected directly from children can document outcomes and assess risk factors throughout the children's lives, and can be compared with children from reference populations; begin data collection with EHRs of children born in the TRICARE system and combine with data from the DoD Birth and Infant Health Registry; collection should be planned at milestones in child's life.
- Biospecimens (blood, urine, semen at a minimum) from HMRP participants will require the identification of appropriate sample collection and storage and equipment (e.g., laboratory facilities and biorepositories) and standardized protocols.
- Ability to link databases and statistical software, particularly VA and DoD EHRs and other records, and potentially other databases will be essential for the HMRP.
- Novel methodologies and efficiencies should be considered for identifying the populations to be sampled and the what and how of data collection and analyses.
- Incentives for recruiting and retaining participants, and reminders to increase response rates (including social media) must be used to increase participation and retention.



# Other Critical Aspects of the HMRP Framework

- Program Management
  - Determine lead organization and possible collaborators (e.g. DoD, NIH, academic research organizations, health care organizations and foundations, state agencies)
- Information technology capabilities
  - Sufficient linkages, storage, and analyses for records from DoD, VA, and other potential participants must be available
- Communication methods
  - Appropriate approaches must be considered, developed, and periodically reviewed and updated, beginning with program initiation and continuing throughout the life of the program. Tailored communication approaches are needed for
    - Program participants (i.e., service members, veterans, partners, and descendants)
    - Collaborators
    - Researchers from various fields such as public health, epidemiology, genetics and epigenetics and toxicology
    - Other interested stakeholders including organizational leadership and Congress

# Implementation of the HMRP

- Leverage ongoing programs
  - Million Veteran Program
  - Millennium Cohort Study (and Family Study)
  - DoD Birth and Infant Health Registry
  - DoD Serum Repository
- Advantages
  - reduced costs
  - expedited data collection
  - access to already engaged study populations
- Periodically evaluate the program goals, activities, and results and make necessary modifications to optimize efficiency and effectiveness of the HMRP

# Pathophysiologic Research Agenda (1)

- Advantages of animal and cellular models versus epidemiologic studies
  - Results are obtained within a shorter period
  - Easier to complete multi-generation studies
  - Can study effects on whole animal, specific organ systems, tissue types, and cell types
  - Controlled genetics and exposures
- Limitations of animal/cellular studies versus epidemiologic studies
  - Species differences in development and response
  - Extrapolation
  - Difficult to simulate range of human exposures

# Pathophysiologic Research Agenda (2)

- Basic and translational research requires:
  - Fit-for-purpose models and reagents for generational studies
  - Validated models appropriate for studying specific exposures
  - Methods and databases for acquiring, curating, and analyzing the resulting datasets
- Reproductive effects research needs include:
  - Windows of susceptibility
  - Dose-response relationships
  - Duration, and co-exposures (mixtures)
- Developmental effects research needs include:
  - Transmission and persistence of effects
  - Gene x environment interactions
  - Modifiers (e.g., stress, diet) of genetic and epigenetic effects

# Moving Forward

- At present there is insufficient evidence to link any deployment exposures to epigenetic effects.
- To better understand the potential for generational effects that may result from a veteran's deployment exposures, scientific priorities to be considered include:
  - Collection, storage, and maintenance of comprehensive baseline and longitudinal data and biospecimens from veterans, their partners, and their descendants;
  - Detailed characterization and assessment of exposures during and after deployment;
  - Development, evaluation, standardization, and interoperability of biomarkers of exposure, susceptibility, and biological effects.
- Committee recognizes that developing and implementing an HMRP is a challenging task, but concluded that with proper scoping and leveraging of existing resources, such a program is feasible.