AIRBORNE HAZARDS RELATED TO DEPLOYMENT

Section V: Research Initiatives

Two researchers conducting laboratory testing.

Photograph: Courtesy of the US Army Public Health Command (Aberdeen Proving Ground, Maryland).

Chapter 27

RESEARCH STUDIES: OVERVIEW AND FUTURE DIRECTIONS

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INTRODUCTION

It has been known that service members deployed to southwest Asia (SWA) are exposed to extremely high levels of airborne particulate matter (PM) since early in Operation Iraqi Freedom/Operation Enduring Freedom.[1] The US Army Center for Health Promotion and Preventive Medicine (now the US Army Public Health Command [USAPHC; Aberdeen Proving Ground, MD]) conducted the Enhanced Particulate Matter Survey Program (EPMSP) that analyzed the ambient concentrations and composition of PM at 15 sites throughout SWA. USAPHC also showed that ambient levels of PM in SWA far exceed US Environmental Protection Agency environmental guidelines, National Institute for Occupational Safety and Health (NIOSH; Washington, DC) and Occupational Safety and Health Administration occupational levels, and military exposure guidelines.[2] Adverse health effects, including cardiovascular and pulmonary diseases, are well-established consequences of exposure to high levels of PM, with aerodynamic diameters of <10 μm (PM_{10}) and especially less than 2.5 μm ($PM_{2.5}$).[3] The severity of the effects depends on the amount and duration of the exposure, the physical and chemical characteristics of the PM, and the health of the exposed individuals. In addition to exposure to high levels of ambient PM in theater, many service members have been exposed to combustion products from burn pits in which shipping materials, and occupational, food, and residential wastes were incinerated. Exposure to the smoke has been associated with dermal and respiratory irritations.[4] Although there is reasonable cause for concern that these exposures might result in long-term adverse health effects, at present there is neither clear evidence that disease is associated with these exposures nor adequate data to develop reliable risk assessments.

In 2004, Shorr and coworkers[5] reported on an 18-case cluster of acute eosinophilic pneumonia with two mortalities among soldiers deployed to Iraq. They were unable to determine a likely cause for the cluster of this rare disease, although ~80% of patients had recently begun to smoke, and acute eosinophilic pneumonia has been reported to be associated with smoking in a small number of cases.[6] One distinguishing feature of this cohort was that all but one of the patients reported exposures to high levels of ambient dust.

In 2011, King and colleagues[7] described a case series of 80 soldiers from Fort Campbell, KY, who were referred to Vanderbilt University Medical Center (Nashville, TN) between February 2004 and December 2009 for evaluation of exertional dyspnea. Forty-nine of these patients received thoracoscopic lung biopsies. All biopsied patients exhibited lung abnormalities, and 38 of the 49 patients were diagnosed as having a rare condition: constrictive bronchiolitis (CB). The CB patients were described as having experienced exposure to dust storms (33/38); exposure to the sulfur fire at the Al Mishraq sulfur mine in 2003 (28/38); as well as exposure to burn pit, human waste, and combat smoke.

Epidemiological studies have suggested that there are modest increases in respiratory symptoms among service members and veterans who have deployed to SWA.[8–10] The Armed Forces Health Surveillance Center (Silver Spring, MD) performed a large epidemiological study of service members stationed in operating bases with and without burn pits, and also performed a study of personnel stationed near civilian incinerators. At most, the study found limited evidence of association between living in proximity to an incineration site and increased risk of adverse health outcomes[4] (see Chapter 6: Epidemiology of Airborne Hazards in the Deployed Environment and Chapter 7: Discussion Summary: Defining Health Outcomes in Epidemiological Investigations of Populations Deployed in Support of Operation Iraqi Freedom and Operation Enduring Freedom).

In contrast, reports in the popular press ascribe diseases in service members and veterans, ranging from cancers to substantial impairments in respiratory function to exposure to PM and burn pit smoke.[11–13] Advocacy groups such as Burnpits 360° (Robstown, TX)[14] and the Sergeant Thomas Joseph Sullivan Center (Washington, DC)[15] also assert that exposures to dust and smoke during deployment to SWA have resulted in ill health of service members and veterans.

In response to concerns about potential health issues arising from inhalational exposures in SWA, a number of working groups (WGs) have been convened in efforts to develop frameworks for understanding risks and developing solutions. The Joint Particulate Matter Working Group, charted by the US Department of Defense, met at the NIOSH in 2005 to investigate potential health issues related to this ongoing PM exposure. The group identified a number of knowledge gaps that included the physical and chemical characteristics of ambient PM in SWA and assessment of its toxicity.[1] In 2010, Dr Cecile Rose (Director, Occupational and Environmental Medicine Clinic) at National Jewish Health in Denver, CO, organized a meeting attended by representatives of the Army, Navy, and Veterans Affairs, as well as private and academic healthcare providers. In addition to considering the state of science related to deployment-related pulmonary health threats, participants also considered approaches for performing surveillance and evaluating respiratory health in the context of deployment. Like the Joint Particulate Matter Working Group, this body concluded that there was not adequate toxicological, epidemiological, or clinical data to adequately evaluate either the scope or severity of adverse effects of inhalational exposures in troops deployed to SWA. Outcomes and recommendations of this meeting are reported and expanded on in a special issue of the *Journal of Occupational and Environmental Health*.[16]

In addition to the WGs previously described, two independent reviews of the state of knowledge about airborne hazards in SWA were commissioned from the National Academy of Science (Washington, DC). The USAPHC commissioned an independent review of the EPMSP by the Committee on Toxicology of the National Academy of Sciences that was published in 2010.[17] Despite the breadth of the EPMSP, the Committee concluded that there was not enough data relating the knowledge of the chemistry and abundance of ambient PM to health effects to provide a foundation for health risk assessment. Similarly, a 2011 report—commissioned from the Institute of Medicine (Washington, DC) by the US Department of Veterans Affairs on the possible effects of exposure to burn pit smoke in Iraq and Afghanistan—failed to find sufficient evidence to evaluate possible risks from exposures to burn pit combustion products.[18]

Following the National Jewish Health Working Group, it was clear that a coordinated effort to resolve issues related to deployment-related respiratory disease would be required because available data were limited, conflicting, and drawn from diverse sources. In response to this problem, a new Pulmonary Health Task Area was proposed by the Military Operational Medicine Research Program (MOMRP; Fort Detrick, MD) of the US Army Medical Research and Materiel Command (MRMC; Fort Detrick, MD) with the support of the MRMC commander. In June 2010 and December 2011, MOMRP brought together diverse groups of experts to examine the current medical and scientific evidence and to formulate an integrated, multidisciplinary research plan to address the issue of deployment-related respiratory disease. These WGs, chaired by the author, included representatives of all four services; the Department of Veterans Affairs; and academic experts in pulmonary medicine, toxicology, pulmonary pathology, occupational and preventive medicine, computer science, and epidemiology. The WGs considered the available scientific, epidemiological, and medical evidence, and provided a gap analysis and recommendations for the prioritization of research.

Although the relevant epidemiological and clinical data are presented elsewhere in this book (see Chapter 6: Epidemiology of Airborne Hazards in the Deployed Environment, Chapter 7: Discussion Summary: Defining Health Outcomes in Epidemiological Investigations of Populations Deployed in Support of Operation Iraqi Freedom and Operation Enduring Freedom, and Chapter 31: Update on Key Studies), the current research discussed herein focuses primarily on data from experimental toxicology studies that are largely complete. This chapter also briefly covers some ongoing research that has not been described elsewhere. The Future Research section of this chapter presents the proposed clinical research summaries of the MOMRP WGs.

CURRENT RESEARCH

A number of research projects have been undertaken by US Department of Defense-funded researchers in response to historical concerns about exposures to PM in SWA and in response to concerns expressed by the WGs. These projects will fall within the scope of future research areas proposed by the MOMRP WGs, but it is worth noting that some of them had already commenced before those WGs met.

Several studies have addressed the toxicity of dusts from SWA. Wilfong and coworkers[19] at the Naval Health Effects Laboratory at Wright-Patterson Air Force Base (now the Naval Medical Research Unit-Dayton; NAMRU-D) exposed rats to PM collected at Camp Buehring, Kuwait. PM was collected inside closed tents from precleaned surfaces and sieved to ≤10 μm in diameter. In addition, PM was suspended in phosphate-buffered saline, and 1, 5, or 10 mg of PM in buffer was injected intratracheally into the lungs of rats. Control exposures were performed with equal masses of titanium dioxide (negative control) and silica (positive control) particles of similar size. Animals were harvested at 1, 3, and 7 days and 6 months postexposure. Based on biochemical, histological, and cell profile data, both the Camp Buehring PM and titanium dioxide particles provoked a mild transient inflammatory response in the lungs that was largely resolved in 7 days and completely resolved in 6 months. Positive control silica particles provoked a lasting inflammatory response that persisted through the 6-month experiment. The authors also examined the histology of the spleen, testis, and kidney, but found no abnormalities attributable to exposure to the PM.

A second study led by NAMRU-D (Dorman et al[20]) investigated the effects of the pulmonary health threats of tobacco smoking and inhalational exposure to PM from Iraq singly and in combination in rat studies. As noted previously, exposure to fine PM is common for service members deployed to SWA, and there is an increased incidence of new-onset and recidivist smoking in active duty military personnel.[21] Rats were exposed to mainstream cigarette smoke or air using a nose-only exposure system for 3 hours/day, 5 days/week for 4 weeks. At this time, rats also began to be exposed to aerosolized silica particles (positive control) or surface soil collected at Camp Victory near Baghdad, Iraq, for 19 hours/day for 2 weeks in whole-body inhalation chambers. Although the soil used in this study was not extensively characterized, it is reasonable to assume that it is substantially similar to the Camp Victory soil analyzed in the EPMSP that contained chiefly clay minerals and low amounts of silica.[2] Soil and silica particles were size fractionated and blown into the inhalation chambers at approximately 1 mg/m^3, with mean aerodynamic diameters of 1.7 and 1.4 μm, respectively.

This study examined a large number of variables, including

- standard clinical parameters,
- plethysmography,
- histopathology,
- bronchiolar lavage biochemistry,
- cell profiles and proteomics, and
- global gene expression in the lung.

Despite the comprehensiveness of this study, few responses attributable to soil particle exposure were identified. Inflammation was minimal in either soil- or silica-exposed animals based on histopathological assessment, although the prevalence of indicators of inflammation was greater in animals exposed to silica. Similarly, gene expression and proteomics data are suggestive of mild inflammation in exposed animals, with silica eliciting somewhat greater responses. No statistically significant differences from control in lung function measures were found for soil- or silica-exposed animals.

The findings with particle exposures alone contrast strongly with the results of mainstream cigarette smoke exposures either in combination with soil or silica particles or alone. Histological lesions, alterations in cell profiles in lavage fluid, reduced body weight, and abnormal plethysmographic results were apparent. Although there was some evidence of interaction between particle and smoke exposures, particularly in the gene and protein expression data, the largest effects throughout the experiment resulted from cigarette smoke exposure. The authors concluded that pulmonary toxicity of the Camp Victory surface soil is qualitatively similar to, but less than, the toxicity of silica.

Two roughly parallel studies, conducted by the author's research program at the US Army Center for Environmental Health Research and NIOSH, attempted to address the toxicity of PM from SWA (A. Jackson, personal communication, 2013) by examining the effects of a single intratracheal instillation in rats of ambient PM collected at Camp Victory. PM was collected using high-volume air samplers designed to capture airborne particles 10 μm in diameter and smaller at Camp Victory during the spring of 2008 and the spring of 2009 by US Army Center for Health Promotion and Preventive Medicine (now USAPHC) personnel. In the first study, rats were exposed to 2.5, 5.0, or 10 mg/kg PM collected in 2008 or a fine, standard, freshly fractured silica (obtained from Dr Vince Castranova at NIOSH) in buffered saline and examined 3, 7, 30, 60, 120, or 150 days later. The control was buffer only. The 2008 dust-exposed animals showed early evidence of inflammation and tissue damage in the lung as judged by cell counts and the presence of lactate dehydrogenase and albumin in the bronchiolar lavage fluid collected from the animals. However, inflammation largely abated in 7 days and was not evident at the longest time tested (120 days). In contrast, silica-exposed animals showed persistent inflammation by these measures up to 120 days. Histological examination of lung tissue from the animals extending to 150 days was consistent with the biochemical and cell profile analyses, and the animals exposed to silica-positive control showed fibrotic and potentially neoplastic changes.

The second exposure study had several aims:

- to determine whether their observations with the 2008 PM were reproducible and whether the ambient environmental dust was similar toxicologically over time;
- to compare the toxicity of the 2008 and 2009 dust samples with a standard reference material that had some similarity to a well-studied US exposure and was less toxic than the silica control typically used in this type of study; and
- to make a head-to-head comparison of the Camp Victory PM with the Camp Buehring dust tested by Wilfong and coworkers (generously provided by V Mokashi, NAMRU-D).

A well-characterized US urban PM (or USPM) collected in the St. Louis, MO, area during the 1970s was selected as a reference material.[22] Rats were exposed by intratracheal instillation to 2.5, 5.0, and 10.0 mg/kg environmental PM in buffered saline. Again, silica served as a positive control, and the buffer served only as a negative control. Histology of lung tissue from the rats was evaluated at 60, 120, and 150 days (silica, 2009 dust, USPM). Because the 2008 Camp Victory and Camp Buehring sample materials were limited, animals exposed to these PMs were examined only at 120 and 150 days.

Results of this follow-on experiment were consistent with the earlier ones. Mild small airway changes (distortion and fibrosis of terminal bronchioles) and centriacinar emphysematous lesions were associated with exposure to all the dusts in this experiment. Emphysematous changes were most severe in animals exposed to the USPM, which has a high combustion product content[22] rather than mineral materials like the Camp Victory[20] and Camp Buehring PMs.[19] Because of the report of CB in troops returning from SWA by King and coworkers,[7] airways 180 to 360 μm in diameter were given careful attention in a reexamination of histological materials. However, no evidence of CB is in the sense of circumferential fibrosis with luminal constriction was observed.

Environmental PM tested from Iraq and Kuwait does not appear to be highly acutely toxic, although repeated exposure might lead to obstructive disease or allergic lung disease (eg, hypersensitivity pneumonitis or asthma in some individuals). However, differences between human and rat anatomies and between experimental rat exposure and environmental exposure conditions experienced by soldiers do not permit definitive conclusions to be drawn.

A number of studies at Brooke Army Medical Center (Fort Sam Houston, TX), funded in whole or in part through MOMRP, have been undertaken in an attempt to determine the prevalence of pulmonary disease in active duty military, develop case definitions, evaluate pre-/postdeployment spirometry for health surveillance, and improve clinical characterization of patients complaining primarily of exertional dyspnea. These studies will not be addressed further here because they are discussed in Chapter 6: Epidemiology of Airborne Hazards in the Deployed Environment, Chapter 8: Pulmonary Function Testing—Spirometry Testing for Population Surveillance, and Chapter 31: Update on Key Studies.

The cluster of CB cases diagnosed at Vanderbilt Medical Center and controversy surrounding them[23,24] highlighted the need for an objective system for diagnosing small airways disease. The MOMRP of the MRMC awarded a 3-year grant to investigators at National Jewish Health and Vanderbilt University to develop a standardized method for quantifying small airways abnormalities. This study is ongoing and has assembled a team of pathologists, established scoring criteria, and prepared test sets of slides for evaluation that include the CB specimens from Vanderbilt Medical School, CB lung samples from the Lung Tissue Research Consortium (National Heart, Lung, and Blood Institute [Bethesda, MD]), and normal lung tissue from the International Institute for the Advancement of Medicine (Edison, NJ).

The possible role of exposure to combustion products from open burn pits in the pathogenesis of a variety of disease states is a matter of some concern to service members and families,[13,14] as well as the military and US Department of Veterans Affairs medical communities. This has been evidenced by the Armed Forces Health Surveillance Center epidemiological study[4] of possible effects of burn pit exposure and by the Institute of Medicine report[18] on the issue commissioned by the Department of Veterans Affairs. In July 2012, according to Commander Daniel Hardt, NAMRU-D had undertaken direct studies to assess the toxicity of burn pit smoke using cell culture exposures to combustion products from reconstituted burn pit material mixtures. Composition of the combustion plume had been analyzed, and evaluation of the toxic responses of the exposed cells was under way. NAMRU-D has recently obtained funding to extend its research to more relevant animal experiments.

In an effort to develop an understanding of the types of lung disease that may be associated with deployment, the Joint Pathology Center (Silver Spring, MD) has initiated efforts to investigate pathologies evident in surgical lung specimens from deployed service members. In March 2013, Dr Michael Lewin-Smith acknowledged that the study would also investigate whether there is evidence of an association between pulmonary lesions and the composition of PM in lung specimens.

In a 2012 presentation to the Pulmonary Health in Deployed Environments In-Process Review, Drs Bora Sul and Jaques Reifman described how the MRMC's Bioinformatics High Performance Computing Software Applications Institute (Fort Detrick, MD), with the assistance of Brooke Army Medical Center, has undertaken a combined computational and physical modeling effort to ascertain whether obstructions and functional alterations in the small branches of the bronchial tree perturb air flow in ways that may be detectable using magnetic resonance imaging. Such an approach could significantly improve diagnostics and potentially reduce the number of thoracoscopic biopsies that are necessary for diagnosis of lung disease.

FUTURE RESEARCH

On June 22–23, 2010 and December 1–2, 2011, the Military Operational Medicine Research Area Directorate convened a WG of military service, Veterans Affairs, and extramural experts to provide direction for a proposed Defense Health Program-funded task area that would manage a structured research effort investigating pulmonary health threats of deployed service members. It should be noted that a few of the studies discussed herein have actually begun since the WGs met. It is currently expected that the task area will be funded and begin studies in federal Fiscal Year 2014.

The WGs were charged with the following:

- identifying data gaps or threats related to respiratory health risks for service members in SWA,
- determining research approaches to address data gaps,
- indicating competencies or capabilities required to address threats, and
- prioritizing efforts to address the data gaps and required competencies.

Both WGs recognized four broad areas of research:

1. clinical studies,
2. animal studies,
3. biomarkers, and
4. epidemiology/exposure assessment.

The WGs also recognized four principal knowledge gaps:

1. disease prevalence and severity,
2. disease screening and diagnosis,
3. toxicity/pathogenicity of PM, and
4. intervention and treatment.

The two WGs reached very similar conclusions, and a consensus is presented here. Proposed and prioritized projects (in order of decreasing priority within sections) are also described. It is expected that the findings of these projects will form the basis for initial decision-making when the task area is implemented.

Clinical Studies

Clinical studies were recognized as foundational for establishing case definitions of deployment-related pulmonary disease and for determining its prevalence and severity. Several types of studies were proposed to address the issue of disease prevalence and severity. A retrospective chart review study and a postdeployment respiratory health study of service members with dyspnea were put forward because they could be rapidly initiated and executed. The postdeployment study could also serve as a pilot/feasibility study for a larger pre- and postdeployment assessment of pulmonary health in deployed service members. Both patient studies would include collecting biosamples for a proposed repository and collecting biosamples for biochemical biomarker discovery, along with patient histories, pulmonary function, and imaging data. A number of these studies have begun, and preliminary findings are described elsewhere in this book.

In addition, provided that data of sufficiently high quality could be collected, a study of indigenous Iraqis who were continuously exposed to the SWA environment might reveal long-term effects that are difficult to discern in deployed service members in the short term. Analysis of lung samples taken at autopsy from deployed service members might reveal undiagnosed and/or subclinical disease that foreshadow later health outcomes.

A final issue was the well-publicized diagnosis of CB in some soldiers by open lung biopsy at Vanderbilt University Medical Center. A careful, independent study of these patients and controls was proposed to assess the association of the morphological features seen in these patients with disease. This study has already begun.

The following nine summary points of the proposed clinical research is provided here in order of decreasing priority (based on a tradeoff of cost, feasibility, and importance for filling the identified data gaps):

1. perform a retrospective chart study of active duty military personnel diagnosed with chronic lung disease;
2. create a registry of all military personnel diagnosed with chronic pulmonary disease (see section on Biomarkers);
3. evaluate postdeployment military personnel with complaints of new-onset dyspnea to determine the etiology of pulmonary disease and the utility of clinical evaluation (see section on Biomarkers);
4. carry out a pre- and postdeployment evaluation of military personnel to determine the incidence of postdeployment disease (see section on Biomarkers);
5. complete a pre- and postdeployment screening to determine whether spirometry can serve as a sensitive measure of underlying lung disease;
6. standardize diagnostic methods for patients with small airways disease, including the CB cases seen at Vanderbilt University Medical Center;
7. perform a review of lung specimens from autopsies to determine whether there is undiagnosed lung disease in deployed, compared with nondeployed, military personnel (if available);
8. evaluate the respiratory health of the native Iraqi/Afghanistan population to determine the incidence and severity of background pulmonary disease; and
9. test whether spirometry and chest X-ray film screening on entry to service can predict lung disease in a longitudinal pre-/postdeployment study.

Animal Studies

Because clinical studies are limited by standard-of-care considerations and are largely descriptive, the WGs discussed a number of animal studies for the direct determination of the toxicity and pathogenicity of PM and sulfur fire combustion products, development of biomarkers of disease, and studies of the mechanisms of pulmonary disease to address the toxicity/pathogenicity and disease screening/diagnosis gaps. In particular, WGs recommended rodent toxicity studies and studies of the pulmonary health of working dogs. The WGs proposed studying the toxicity of PM from several localities and the effects of repeated PM exposures. Several of these studies have begun and have been described previously.

The WG also proposed examining the pulmonary health of deployed working dogs exposed to the same environmental conditions as deployed service members over substantial periods of time. The dogs receive comprehensive veterinary workups, and a large number of tissue samples collected at necropsy are available. During checkups or at necropsy, collection of biosamples for biomarker studies may be possible.

Both the dog and rat populations are more homogeneous than humans and are likely to support small studies with useful statistical power.

The following five summary points of the proposed clinical research is described here in order of decreasing priority:

1. determine the toxicity/pathogenicity of ambient SWA PM collected from multiple sites in rat single intratracheal instillation studies;

2. complete a longitudinal study of the pulmonary health of working dogs,
3. perform a lung necropsy study of deployed/non-deployed working dogs for toxicity and pathology,
4. carry out experiments with repeated exposures of rats to PM from SWA to test the toxic effects of chronic exposure in contrast to single exposure studies, and
5. determine the mechanism and pathogenesis of lung injury using a known lung toxicant (eg, crystalline silica).

Biomarkers, Biosample Repository, and Chronic Pulmonary Injury Registry

Practically speaking, the biomarkers focus area cannot readily be separated from the clinical and animal studies that will provide the samples and raw data for its studies. However, the research methods and aims are sufficiently different to warrant a separate discussion. Data and samples will be acquired from the clinical and animal studies described herein.

Developing biomarkers to improve the diagnosis of pulmonary disease and to monitor disease progression was recognized as a high priority need for both the disease prevalence and severity gap and the disease screening and diagnosis gap. Two types of biomarkers were identified: (1) molecular and (2) physiological. Molecular biomarkers are biochemical entities; ribonucleic acid molecules; proteins; or small molecules that can be measured in blood, bronchoalveolar lavage fluid (BALF), or other biological matrices to improve diagnosis and monitor disease progression. Physiological biomarkers represent information derived from functional measurements of the mechanics or effectiveness of respiration. Such biomarkers would be based on pulmonary function tests, impulse oscillometry, bronchoprovocation, or other functional or mechanical data sources.

A prospective registry of data from current military personnel with diagnosed postdeployment lung disease and a repository for biosamples were also recognized as high priority needs. The registry would permit tracking the progression of disease and could be potentially mined for common factors associated with the development of respiratory disease. A biosample repository containing samples from individuals in the registry and from clinical studies (eg, postdeployment evaluations of dyspneic service members or pre-/post-deployment evaluations of military personnel) could provide materials for biomarker validation and, potentially, even discovery since the emergence and diagnosis of progressive pulmonary disease could be delayed for months or years. Relevant biosamples could include blood, urine, and BALF. The registry of patients with chronic respiratory disease should include deployment and occupational history, as well as demographic and clinical data (including high-resolution computed tomography scans, baseline pulmonary function tests, and physical fitness test data).

The following four summary points of the proposed clinical research is described here in order of decreasing priority:

1. establish a prospective US Department of Defense registry, including current military personnel with diagnosed postdeployment lung disease and a biomarker repository (see section on Clinical Studies);
2. identify/validate molecular and physiological biomarkers of disease and disease progression in military personnel participating in the postdeployment STAMPEDE 1 (Study of Active-Duty Military for Pulmonary Disease Related to Environmental Dust Exposure-1) study of service members with dyspnea using biosamples and physiological data (see section on Clinical Studies);
3. identify/validate molecular and physiological biomarkers in a pre-/postdeployment clinical study of service members with a comprehensive pulmonary evaluation using physiological measurements and biosamples (see summary point 2; also see section on Clinical Studies); and
4. identify candidate molecular and physiological biomarkers of lung injury and disease progression in BALF, blood, urine, and physiological measurements in controlled lung injury studies in rats (see section on Animal Studies).

Epidemiology/Exposure Assessment

Because the Clinical Studies focus area does not have the ability to examine large numbers of service members, epidemiological and exposure assessment methods are required to capture subtle and rare effects of deployment on respiratory health. In addition, by taking advantage of existing databases (eg, the Millennium Cohort Study, Military Health System, TRICARE, and The Total Army Injury and Health Outcomes Database) with time depth, a historical perspective on pulmonary disease diagnoses among service members can be generated. Building on the historical perspective, prospective continuing epidemiological studies may provide insights into the chronicity of deployment-related respiratory disease. Thus, the Epidemiology/Exposure Assessment focus area provides expeditious and cost-effective tools for identifying possible associations among deployment, disease, and PM exposures.

The WGs proposed several Epidemiology/Exposure Assessment studies to address the identified data gaps. A retrospective overview of pulmonary health in deployed

service members could be developed to serve as a baseline for contemporary and prospective evaluations of respiratory disease related to deployment. Possible adverse effects of PM exposure on deployed service members could be examined by linking demographic and personnel details with medical information in the Military Health System (MHS; inpatient and outpatient data, TRICARE encounter data) to PM and other exposure data (country of deployment, proximity to large burn pits). Because the Millennium Cohort Study is planned to extend until 2022, studies to evaluate the chronicity of deployment-related disease that extend well beyond the limits of the active military career could be performed. Although none of the currently available resources addresses all possible service members—eg, Reserve and National Guard members are underrepresented—and none of the databases contain all service member information, the WG considered that there was a sufficient wealth of facts and figures relevant to the data gaps that the epidemiology and exposure assessment will play critical roles in eliminating the identified knowledge gaps.

The following five summary points of the proposed clinical research is described here in order of decreasing priority:

1. examine historical trends in ICD-9 (*International Classification of Diseases, Ninth Revision*) pulmonary diagnoses among active duty US Army soldiers since 1985;
2. perform a historical prospective study of service member post-deployment, and examine the relationship between PM exposures, deployment, and pulmonary disease using USAPHC surveillance data, MHS healthcare (ICD-9 pulmonary diagnostic codes), personnel, and deployment records;
3. complete a study of the relationship between PM exposures, deployment, and pulmonary health using USAPHC surveillance data, MHS, deployment, and personnel records for active duty participants in the Millennium Cohort Study;
4. perform a 10-year longitudinal study to establish the chronicity of pulmonary disease in deployed service members using USAPHC PM surveillance data, MHS, personnel, and deployment records for participants in the Millennium Cohort Study; and
5. develop and validate an improved exposure assessment survey instrument to more effectively identify exposures and high-risk service members.

SUMMARY

These WGs and independent committees reached substantially consonant conclusions about the state of knowledge of health risks associated with exposure to ambient PM in SWA. The MOMRP Pulmonary Health Task Area Working Group identified four major data gaps:

1. prevalence and severity of deployment-related disease,
2. methods for diagnosis and screening,
3. intervention and treatment, and
4. toxicity and pathogenicity of SWA PM.

The WG also proposed priorities for research in four specific focus areas:

1. clinical research,
2. animal models of toxicity,
3. biomarkers, and
4. exposure assessment.

As new information emerges from ongoing research in both the military and civilian settings, it is certain that the details of the broad research plan described herein will be adapted to account for that new knowledge. Nevertheless, the program as currently envisioned, seems to be well designed to provide answers to critical questions related to airborne hazards experienced by service members deployed to SWA.

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REFERENCES

1. Weese CB, Abraham JH. Potential health implications associated with particulate matter exposure in southwest Asia. *Inhal Toxicol*. 2009;21:291–296.

2. Engelbrecht JP, McDonald EV, Gillies JA, Jayanty RK, Casuccio G, Gertler AW. Characterizing mineral dusts and other aerosols from the Middle East. Part 1. Ambient sampling. *Inhal Toxicol*. 2009;21:297–326.

3. Davidson CI, Phalen RF, Solomon PA. Airborne particulate matter and human health: a review. *Aerosol Sci Technol*. 2005;39:737–749.

4. Armed Forces Health Surveillance Center. *Epidemiological Studies of Health Outcomes Among Troops Deployed to Burn Pit Sites*. San Diego, CA: The Naval Health Research Center (and the U.S. Army Public Health Command–Provisional, Edgewood, MD); May 2010.

5. Shorr AF, Scoville SL, Cersovsky SB, et al. Acute eosinophilic pneumonia among US military personnel deployed in or near Iraq. *JAMA*. 2004;292:2997–3005.

6. Galvin JR, Franks TJ. Smoking–related lung disease. *J Thorac Imaging*. 2009;24:274–284.

7. King MS, Eisenberg R, Newman JH, et al. Constrictive bronchiolitis in soldiers returning from Iraq and Afghanistan. *N Engl J Med*. 2011;365:222–230.

8. Smith B, Wong CA, Smith TC, Boyko EJ, Gacksetter GS, Ryan MAK. Newly reported respiratory symptoms and conditions among military personnel deployed to Iraq and Afghanistan: a prospective population-based study. *Am J Epidemiol*. 2009;170:1433–1442.

9. Szema AM, Peters MC, Weissinger KM, Gagliano CA, Chen JJ. New-onset asthma among soldiers serving in Iraq and Afghanistan. *Allergy Asthma Proc*. 2010;31:67–71.

10. Abraham JH, DeBakey SF, Reid L, Zhou J, Baird C. Does deployment to Iraq and Afghanistan affect respiratory health of US military personnel? *J Occup Environ Med*. 2012;54:740–745.

11. Kennedy K. Balad burn pit harmed troops living 1 mile away. *Army Times*. January 23, 2010. http://www.armytimes.com/news/2010/01/military_burn_pit_011810w/. Accessed September 19, 2010.

12. Kennedy K. Lung disease of soldier linked to burn pits. *Army Times*. July 2, 2009. http://www.armytimes.com/news/2009/06/military_burnpits_lungs_063009w/. Accessed September 19, 2010.

13. Peeples L. Gulf war syndrome, other illnesses among veterans may be due to toxic environments. *The Huffington Post*. February 7, 2013. http://www.huffingtonpost.com/2013/02/07/gulf-war-syndrome-veterans_n_2634838.html. Accessed February 22, 2013.

14. Burnpits 360° website. *Invisible Wounds of Toxic Exposure*. http://burnpits360.org. Accessed February 22, 2013.

15. Sergeant Sullivan Center. *He Found a Diagnosis, Solving a Medical Mystery for Veterans: Dr. Robert Miller: Excellence in Post-deployment Health*. http://www.sgtsullivancenter.org/press-release-dr.robert-miller.html. Accessed February 22, 2013.

16. Teichmann R. Health effects of deployment to Afghanistan and Iraq. *J Occup Environ Med*. 2012;54:655–764.

17. National Research Council. *Review of the Department of Defense Enhanced Particulate Matter Surveillance Program Report*. Washington, DC: National Academy Press; 2010: 10–11, 51–56.

18. Baird CP. Review of the Institute of Medicine report: long-term health consequences of exposure to burn pits in Iraq and Afghanistan. *US Army Med Dept J*. 2012;July–Sept:43–47.

19. Wilfong ER, Lyles M, Tietcheck R, et al. The acute and long-term effects of Middle East sand particles on the rat airway following a single intratracheal instillation. *J Toxicol Environ Health A*. 2011;74:1351–1365.

20. Dorman DC, Mokashi V, Wagner DJ, et al. Biological responses in rats exposed to cigarette smoke and Middle East sand (dust). *Inhal Toxicol*. 2012;24:109–124.

21. Poston WS, Taylor JE, Hoffman KA, et al. Smoking and deployment: perspectives of junior enlisted US Air Force and US Army personnel and their supervisors. *Mil Med*. 2008;173:441–447.

22. National Institute of Standards and Technology. *Standard Reference Material 1648a [Certificate of Analysis]*. Gaithersburg, MD: 2012.

23. Morris MJ, Zacher LL. Constrictive bronchiolitis in soldiers [letter]. *N Engl J Med*. 2011;365:1743–1745.

24. Kushner WG. Constrictive bronchiolitis in soldiers [letter]. *N Engl J Med*. 2011;365:1744.