**State of the Science Workshop to Discuss Environmental Health and Protection:
Personalized Tools to Support Potential and Actual Health Hazards in the Megacity
Operational Environment**

**The Johns Hopkins University
Applied Physics Laboratory**

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**Summary prepared by: JHU/APL Team
Kathlyn Santos, Ph.D.
Kathleen Verratti
Olivia Tiburzi
Chris Bradburne, Ph.D.**

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1. EXECUTIVE SUMMARY

To provide a forum to explore recent scientific advances in understanding several issues related to the development of health risk assessment and surveillance tools in the operational environment (OE), The Environmental Health Program (EHP) at the U.S. Army Center for Environmental Health Research (USACEHR), in collaboration with the Johns Hopkins University Applied Physics Laboratory (JHU/APL), conducted a two-day workshop held at Fort Detrick, Maryland on 27 – 28 October 2015.

The workshop brought together stakeholders, end users, and multidisciplinary subject matter experts (SMEs), including academic researchers, physicians, and military operational medicine (MOM) personnel, to convene on the current science behind prevention, treatment, and delivery of operational medicine associated with occupational health hazards. This provided a forum for participants to interact, share experiences and insight, and to help advance the knowledgebase for potential improvements and appropriate decision making at every level, in order to guide the development of strategic plans and direction for research initiatives.

The JHU/APL has been tasked to assist USACEHR in developing strategic plans and direction for environmental health research initiatives. A first step towards achieving this goal was to co-lead a strategic direction workshop that focused on the following three overarching themes/sessions:

1.) Critical evaluation of realistic, abundant, and probable chemical threats in the megacity OE
2.) The use of far-forward diagnostics in non-agent toxic industrial chemical and materials (TIC/TIM) exposure scenarios and biomarker identification.
3.) Personalized medicine solutions for environmental health and protection.

Session 1 chairs, CPT Blair Dancy and Mr. Steve Patterson, introduced and described the topic of TIC/TIM threats related to the megacity OE. MAJ Jonathan Stallings opening remarks provided observations regarding TIC/TIMs and megacities, and strategically laid out the needs and gaps as they relate to sampling, analysis technologies, and biomarker discovery, in order to predict and respond to exposures. COL Mark Ireland acknowledged in his brief that megacities are diverse; no two are the same. There are pervasive pollutants and the environment, at times, is not conducive, proving difficult to maneuver and making exposures unpredictable. Dr. Skip Kingston brought a perspective of the impact of the human exposome, including all human environmental exposures from conception to present, and how it could play a role in predicting outcomes of exposure.

Session 2 chairs, Dr. Danielle Ippolito and Dr. Charles Young covered capability gaps on biomarker identification and detection capabilities for environmental threats. Dr. Colleen Baird briefed a historical perspective on environmental monitoring and touched on challenges for health surveillance, as it relates to biomarker discovery and sensors. Dr. Ed Perkins followed with a presentation about a novel approach on the application of adverse pathways related to exposures and their impacts on health. Dr. Camilla Mauzy's remarks touched on the challenges involved in biomarker discovery from practical experiences. Dr. Ellen Silbergeld followed with a presentation about exploring the microbiome and the impact on environmental toxicology and biomarker discovery.

For the second day, Session 3 chairs Dr. Christopher Bradburne and Dr. John Lewis covered current states of personalized medicine and their potential use for measuring and mitigating individualized susceptibility to environmental hazards. Ms. Carrie Blout presented research findings from the MedSeq project and the

issues regarding genetic information and its utility. Dr. David Valle introduced the concept of "individualized medicine" and the implications of genetic and environmental variations on human physiology. Dr. David Graham showed findings from his research t in deployable solutions for sampling (sample-prep) that allow multiple tests to be done from one stored sample; additionally, the impact of having bio-repositories was discussed. He also presented information on a newly developed blood-based sampling technology to assist in this effort.

A series of Panel Discussions followed the session presentations where multiple questions-answers and relevant comments were candidly captured. Overall, four major capability gaps in the megacity OE include:

1) *Overall consensus among participants was that prioritization of TIC/TIM threats that are present in the OE is critical*
   In order to provide for actionable results, the major need is to identify TIC/TIMs before we start developing diagnostics capabilities.

2) *Far-forward longitudinal biological monitoring on the individual soldier was highlighted as a critical focus for DoD.*
   These devices need to be portable and easy to use across multiple sample matrices. Another aspect participants identified as instrumental was the need for a pre-deployment medical assessment that establishes baseline for soldier environmental monitoring.

3) *Development of devices for biological monitoring of both the soldier and the environment for a potential threat or exposure event is critical, both pre- and post-deployment.*
   A recommendation was the use of an application that has a secure database to provide additional information on the OE, aiding in the mitigation of an exposure event. Adverse Outcome Pathways (AOPs) could also be used to identify biomarkers of exposure.

4) *Another recommendation centered upon using personalized medicine to identify susceptibility factors for individual soldiers as a means to guide or aid planning and strategic, mission-based decisions for maneuvers.*
   It was mentioned that personalized medicine, as a tool, could inform prevention of exposure for susceptible soldiers or predict the outcome after an exposure event. However, there is still a major ethical component that needs to be overcome with associated genetic information, especially as it relates to policies and procedures.

In conclusion, the workshop brought together leading experts in military environmental health to address the needs within the current and future OE, better clarify environmental hazards, and establish the ground work for the advent of individualized medicine tools to mitigate those threats.

2. BACKGROUND

The mission of the U.S. Army Center for Environmental Health Research (USACEHR) is to develop surveillance capabilities to detect, assess, and prevent health effects from adverse environmental, physiological, and psychological exposures (http://usacehr.amedd.army.mil). USACEHR has built capabilities to address this mission around the areas of environmental health, systems biology, and pulmonary health, and actively works across a broad spectrum of areas from basic research to translational

applications. Currently, the world of general biological science and digital technology is rapidly advancing with new and disruptive technologies that are emerging very quickly. At the same time, the OE for the military continues to evolve. As such, planning and re-evaluation must be performed to ensure that the basic and translational research completed today will be impactful for the OE of tomorrow.

Given the needs within the capabilities mentioned above, USACEHR and JHU/APL collaborated to hold a "State-of-the-Science" (SoS) workshop to focus on three main issues:

1.) The current and future OE threats.
2.) The current and future state of far-forward sensors for TICs/TIMs and far-forward diagnostics for biomarkers of host response.
3.) The advent of personalized medicine tools in the field and how they could be employed to prevent or mitigate individual warfighter susceptibilities.

The goal of this workshop was to bring together the military environmental health community from across the professional spectrum, which encompassed basic researchers, planners, end users, policy-makers, stakeholders, clinicians, preventive medicine specialists, and technologists. Presentations and panel discussions addressing leading-edge scientific issues, topics, and scenarios on the three areas listed above, allowed for the collection of employable information. The overarching goal of the workshop was to facilitate scientific discussions of these issues and the scientific challenges they pose for the assessment of health hazards associated with TICs/TIMs. The anticipated end products of the workshop are three (3) stand-alone manuscripts. The manuscripts will describe the State of the Science for each of the three session areas, in order to communicate a clear research strategy for military decision makers over the next 10 years.

3. WORKSHOP FORMAT

The workshop was divided into three different sessions (see Background and Overview sections) to address the environmental health initiatives. During the sessions, the military and civilian researchers described current efforts related to their areas of expertise. Participants discussed the challenges and opportunities facing stakeholders, end users, and researchers that relate to the needs posed by the OE, as well as the potential tools and advancements that require improvement. On the second day, during the afternoon, participants actively engaged in small, rotating-work-group discussions. The purpose was to provide a more favorable environment for open discussions. The groups shared a distribution of participants with diverse backgrounds across organizations and expertise.

A survey was also posed for participants to exchange information, but a limited number of participants (9 out of 53) filled out portions of the survey. Nonetheless, the information was compiled in the Survey section of this document.

4. OVERVIEW

The USACEHR State-of-the-Science workshop was attended by 58 participants at Fort Detrick. The organizations represented during the workshop included multiple organizations of the U.S. Army, including program managers and senior scientists from the Engineering Research and Development Center (ERDC), the Commander of the Medical Research Institute of Chemical Defense (ICD), environmental engineers and Program Managers from the Public Health Center (PHC), Director of the Military

Operational Medicine Research Program from the Medical Research Material Command (MRMC), Chief of the Public Health Division at the Office of the Surgeon General Office (HQDA), Army Research Laboratory (ARL), Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD), Health Readiness Center of Excellence (CDD), the Commander, Deputy Commander, Principal Investigators, Director, Task Manager, and Executive Officer from the Center for Environmental Health Research (USACEHR). Along with members of the U.S. Army, the Chief of Personalized Medicine with the U.S. Air Force Medical Support Agency (AFMSA) and the Chief Health Strategist of the office of the Air Force Surgeon General also attended the workshop. The workshop also included nonmilitary representatives from John Hopkins Bloomberg School of Public Health (JHSPH), Johns Hopkins Medical Institutes (JHMI) and the Harvard Medical School, Brigham and Women's Hospital, Duquesne University, and the Johns Hopkins University Applied Physics Laboratory (JHU/APL).

Appropriate decision-making at every level requires the integration of multiple types of data. In order to gain an understanding and focus on the issues that the USACEHR deemed relevant for their mission, the workshop addressed the following objectives:

1.) ***Critical evaluation of realistic, abundant, and probable chemical threats in the dense, urban OE (i.e., Megacities).*** This topic focused on methods to prioritize diagnostic/prognostic indicators of adverse health effects after exposure to non-agent TICs/TIMs.
2.) ***The use of far-forward diagnostics in non-agent toxic industrial chemical and materials (TIC/TIM) exposure scenarios.*** This topic addressed how to prioritize health effects that need far-forward diagnostics in the Megacity OE, as well as existing technologies and diagnostic tools that should be advanced far forward. The topic of AOPs for biomarker identification was also addressed.
3.) ***Personalized medicine solutions for environmental health and protection.*** This session focused on personalized medicine and the impact on environmental health and protection (EH&P) in the military. Research initiatives and/or capabilities that need to be developed to promote personalized medicine in EH&P, and how these capabilities must be adapted to unique military-specific exposure scenarios, were also considered.

The two-day workshop was used as a forum to engage selected representative stakeholders and subject-matter experts (SMEs) from multiple organizations, in order to participate in discussions to identify the current needs, gaps, and limitations, along with courses of action, information systems, and data indicators relevant to the impact of threats in the OE.

4.1 Session 1: TIC/TIM Threats Related to the Megacity Operational Environment

Note: The following information is presented as abstracts from the various SME presentations

4.1.1 Introduction

Session chairs, CPT Blair Dancy and Mr. Steve Patterson, introduced and described the topic of TIC/TIM threats related to the Megacity OE. It is predicted that by the year 2030 there will be 41 megacities with over ten million inhabitants each, which comes to about 66% of the world's population living in a Megacity. This trend towards urbanization of the world's population has created concern surrounding future planning and operations, specifically in the context of deployment and surveillance. The fast population growth in some of these megacities has created many concerns for public health, as well as

challenges for operations. Some intelligence requirements for operating in a Megacity OE include infrastructure knowledge, environmental threats, and generic public health concerns, such as sanitation. There is a great need for the development of detection tools, both for environmental threats, as well as for medical surveillance for the detection of exposure events. TIMs are a broad category of materials that threaten environmental health and contain a smaller subset of toxicants, called TICs. TICs and TIMs pose a continuous threat to public health and U.S. forces. The number of TICs/TIMs that exist is exceedingly high, and in order to address the issues surrounding them, we need to begin by prioritizing which toxic chemicals and materials pose the most significant threat.

4.1.2 Presentations

MAJ Jonathan D. Stallings: Introduction to USACEHR's Environmental Health Program Workshop Issues

In the opening remarks, MAJ Stallings discussed the topic of TICs/TIMs.

> *According to JP 3-11, a toxic industrial material (TIM) is a generic term for toxic, chemical, biological, or radioactive substances in solid, liquid, aerosolized, or gaseous form that may be used, or stored for use, for industrial, commercial, medical, military, or domestic purposes. A toxic industrial chemical (TIC) is a chemical developed or manufactured for use in industrial operations or research by industry, government, or academia that poses a hazard.*

MAJ Stallings also introduced issues that the USACEHR needs to address for their health research initiatives and how efforts in far-forward diagnostics, biomarker discovery, and personalized medicine tools might impact the outcomes. There is a need for new sampling and analysis methodologies for TICs/TIMs, as well as for biomarker discovery, in order to predict and respond to exposure susceptibility. Personalized medicine has the potential to aid in this ongoing effort. TICs/TIMs pose a threat to service members across a broad range of missions and it is essential to develop protection against potential and actual exposures. In a recent study, over a ten-year period, there were 585 documented hospitalizations due to toxic substance exposure. Although this number seems small, it is predicted to increase as service members are deployed to urban areas.

There are concerns among service members about the long-term health effects from certain exposures during deployment. Specifically, poor air quality, due to trash incineration, smoke from burning oil, geological dust, as well as exhaust and industrial byproducts are significant issues. An effort began, in 2000, to focus on the state of current and future strategies to protect the health of deployed U.S. forces. Efforts included environmental sampling, geographical location identification, and biological activity data collection to improve risk assessment. Several findings were noted, including a lack of appropriate medical follow-ups, gaps in data from individual biomonitoring, and poor characterization of adverse health effects. The overall impression was that many threats were identified, but very few solutions have been introduced.

In 2010, a symposium, comprised of experts in the field of preventative medicine, was held, focusing on rare and unanticipated environmental exposure events. The specific focus of environmental exposure episodes included oil wells and water treatment facilities. Lessons learned from this symposium included that an increase in medical awareness could prevent exposures, for instance providing proper protective equipment (PPE) during exposure events could avoid many routine exposure scenarios. Many gaps were identified that prevent the necessary support needed for Health Risk Management. Some of these gaps include inadequate occupational environmental health (OEH) sampling and detection equipment,

inefficient/ineffective lab testing, inadequate tracking, identifying, planning, and production in IT systems, as well as a lack of integration of health data and medical readiness status. It is of paramount importance to develop solutions for these capability gaps.

The goals for this current workshop were to focus on finding solutions for the gaps found in the 2010 symposium, but tailored to OEH issues related to the Megacity OE. Some specific goals include improved medical awareness, improved tools for sample collection, analysis, data dissemination, and improved environmental surveillance tools that can integrate sampling and health risk assessment. Ultimately, improvements need to be made in health surveillance that provides actionable information that is achievable. For instance, incorporating our understanding of individual resiliency in the role of exposures, and developing disease risk models to explore host response, will improve our understanding of the routes of exposure, susceptibility factors, resiliency, and the genetic makeup of the host. Additional goals for this workshop include identifying and prioritizing threats and identifying what support is needed for diagnostics. The workshop focused on both external and internal components of hazardous environmental exposures.

There are many considerations to take into account regarding exposure and its relevance to the military. These considerations can be divided into a simulated timeline of an exposure event, including protective measures pre-exposure, counter effects post-exposure, as well as continued acute care and treatment of long-term effects post-exposure. By quickly glancing at each of these time points, there are obvious gaps and room for improvements across the temporal spectrum of care. For example, with pre-exposure, we can protect our soldiers by equipping them with proper PPE, but also educating service members on sampling techniques and symptomology identification. Some questions we need to answer for pre-exposure measures include what kind of medical awareness can we bring to bear, prior to potential exposures, as well as how do we establish baseline sampling and improve monitoring capabilities? As for questions that need to be addressed post-exposure, some of these include countermeasures, treatment, and sample collection. For instance, specifically at time of the exposure, how would you collect a sample and get it back to the lab to help establish individual baseline data? Additionally, how do you obtain follow-up data post-exposure, and how do we archive and actionably use these data to inform others? How do we use biomarkers to determine treatment post-exposure? Overall, the number of gaps in knowledge, products, and policies, makes it impractical to address these issues s one chemical at a time. Some of the most relevant developments being considered pre-exposure include particulate matter and chemical dosimeters. No single device has been identified that is capable of monitoring the entire spectrum of environmental threats. There is some work being done to identify and to monitor biomarkers post-exposure, but how can these data be used for early detection?

Currently, there are many exposure tests that target one chemical at a time that are expensive and generally used for situations where there are known exposure threats. Another approach that may improve upon detection during post-exposure would be to examine the host response by looking at changes in biomarkers. The Department of Defense has a serum repository that could be leveraged to establish baselines and look at physiological changes pre- and post-deployment. Existing data about host response, health effects, and individual sensitivities are limited to research done on drug toxicity, and often there are limited data on specific TICs/TIMs. The problem is complex and difficult due to the number of TICs/TIMs, as well as the experimental limitations of animal studies. Ideally, because of the complexity of this problem, the technology that is developed should be chemically agnostic and multiplexed, portable, integrative, and capable of testing multiple sample types, including blood, saliva, and urine.

There is a large focus on the use of AOPs to identify and understand biomarkers that are early indicators of exposure. In order to identify these biomarkers, a review of large amounts of drug toxicity data, and their relevant health effects, is needed. Another way to reduce the complexity of this problem is to prioritize the health effects from toxic chemicals by looking at their frequencies and understanding how the chemicals affect health. However, there are limited data for health effects on the central nervous system (CNS) and pulmonary systems, which is of significant concern to the military. When it comes to *in vivo* studies in animals, about 70% of toxicity findings translate to relevant human toxicity. There are large-scale data available from liver damaged by drug toxicity. Specifically, the USACEGR has identified changes in co-regulated gene clusters that correlate to health effects in the liver and kidneys. There may be some similarities in how TIC exposures affect health and regulate genes. In conclusion, literature-based bioinformatics, and data mining approaches helped to identify and qualify biomarkers that are predictive of early toxicity. AOPs are critical to identifying relevant biomarkers.

Col Mark A. Ireland: Megacities and Environmental Health

Col Mark Ireland followed with an overview of megacities and the impact of those environments on exposures. Over the past 100 years there has been an urbanization trend with migration towards cities. There is an increasing number of megacities in underdeveloped countries, mostly in coastal regions. Because of location, population density, and lack of infrastructure due to underdevelopment, the odds of catastrophic disasters are higher in these areas. If an event, natural or not, occurs in an allied megacity, the U.S. Army needs to be able to mitigate risks that include environmental exposures, in order to protect service members when operating in that environment. Considering that there are huge differences between existing and developing megacities, predicting and mitigating these risks is a very complex problem. The fastest growing megacities tend to be in underdeveloped nations that face many challenges resulting from population growth including rudimentary issues, such as sanitation. Additionally, the risks increase as the level of development in a megacity decreases. . Many questions arise when asking how prepared is our military for such OEs, particularly how could we become better prepared? The developing megacities not only pose a threat to soldiers who may be operating in the environment, but they have a massive impact on climate change. The environmental pollution produced by these megacities ultimately affects the world's air, water, and food resources. Water security is a concern, especially given how it impacts farming, agriculture, and its potential for a breeding ground of vectors such as mosquitos. Many urban environments, especially in developing countries have small, local markets where food is exposed to contamination. Faced with the problems mentioned above, there is a great need for new technologies that can rapidly assess water and air quality. These capabilities could prevent exposures, help to identify those that do occur, and help to protect service members.

Dr. Skip Kingston: Metrology of Environmental Human Health Assessment

Dr. Kingston presented research on the impact of the human exposome and how it could play a role in predicting outcomes of exposure. The human exposome is the complete genome, including all human environmental exposures from conception to present. There is very little known about what role the exposome plays in non-communicable diseases (NCDs) and how it affects overall health. The World Health Organization (WHO) has done studies on NCDs and believes some may be caused by toxic exposure, especially diseases like cancer and chronic respiratory diseases. There is a presence of persistent organic pollutants in megacities where environmental protection laws are lacking. These persistent organic pollutants affect every physiological system in the body and have been found in serum samples from

patients with NCD's, such as heart disease, diabetes, autism, lupus, Alzheimer's, and multiple sclerosis. There is a list of 10 specific chemicals that are suspected of causing autism spectrum disorders (ASD), asthma, attention deficit hyperactivity disorder (ADHD), and premature birth. Dr. Kingston conducted a study on 30 children with autism and 30 control subjects that were all screened for 406 molecular variables from blood samples. 100% of all the toxic compounds that the subjects were screened for were found in their blood. However, when the children with autism were compared to the control subjects, significant differences were found in the levels of certain toxins, specifically magnitudes higher in the children with ASD when compared to the controls. Recently, at least 20 biomarkers have been causally linked to ASD. When two species of glutathione, GSH and GSSG, exist is specific ratios, this may support an ASD diagnosis and supporting treatments. The immune system works best when there is a balance of GSH and GSSG, and in ASD children, there is a massive difference in this ratio between them and non-ASD children. When examined closer, it looks like there is nothing in common between the immune systems of children with ASD and non-ASD children. Another ASD predictive indicator is the presence of methylmalonic acid. High levels of methylmalonic acid were 100% predictive of an ASD diagnosis. These two examples highlight the importance of looking at the exposome for biomarkers relating to NCDs, which could be applied to TICs/TIMs as well, and could potentially lead to NCDs like cancer, heart disease, and chronic respiratory diseases in our troops.

4.1.3 Panel Discussion

*Note: Please see "Panel Discussion **section 4.2.3**." Due to time limitations, there was a <u>joint panel discussion</u> addressing topics from Session 1 and Session 2.*

4.2 Session 2: Using Far Forward Diagnostics in Non-Agent Chemical Exposure (TIC/TIM) Scenarios

Note: The following information is presented as abstracts from the various SME presentations

4.2.1 Introduction

Session chairs, Dr. Danielle Ippolito and Dr. Charles Young, covered capability gaps on biomarker identification and detection capabilities for environmental threats. There are a variety of different methods for biomarker detection, including assays that are approved for diagnostic purposes. The technologies that facilitate these detection methods and assays are mostly robotic and fairly large. Currently, the smallest FDA approved devices are approximately the size of a breadbox. For example, the Quest Fibrosure Assay is a blood test that looks at six different biomarkers with 95% accuracy for diagnosing liver disease. However, this test is much more complex and does not just give a positive or negative result, therefore algorithms are needed to reach a conclusion, making it not very far-forward or ideal for less specialized users. Medical concepts of operations (CONOPS) can be divided into 4 categories, including role 1 (soldier to soldier treatment), role 2 (medical companies with limited laboratory diagnostics), role 3 (combat support hospitals), and role 4 (large hospitals providing definitive care). Most diagnostics currently take place in role 3 combat hospitals, due to the size and power requirements of the devices that are currently available. There is a need for a device that can be used in role 2 environments. In order for a device to operate in a mobile treatment facility, it must be Clinical Laboratory Improvement Amendments (CLIA) waived or have little risk for an erroneous result, as well as provide a simple actionable result of yes or no. Additionally, this device must be able to easily read and use more accessible samples, such as

blood, saliva, or urine. The size of the device should also take into account any reagents and consumables needed for running the assays, ultimately making it a man-portable system. Logistically, the assays run on these diagnostic devices need to be stable at ambient temperature over long periods of time. The devices themselves must be able to run on a single battery charge in case the generator power source is lost, which may not be of the same quality as found at a fixed facility. Ideally, the sample preparation should be automated to reduce training requirements, provide consistent results, and reduce risk of contamination. Currently, there is a trend towards lab-on-chip technology. Generally, these devices are hand-held, battery operated, shock, vibration, and temperature resistant, single-plexed, and produce fast results. Ideally, for these diagnostic systems, all components will be CLIA waived. However, for instruments like the iSTAT, only the device and some assays are CLIA waived. It appears as though systems like the iSTAT are the way of the future. However, there will be challenges convincing companies to create assays for biomarkers that are uniquely relevant to the military population and not the general public.

4.2.2 Presentations

Dr. Colleen Baird: Using Far Forward Diagnostics in TIC/TIM Scenarios

Dr. Colleen Baird briefed a historical perspective on environmental monitoring and touched on challenges for health surveillance regarding biomarker discovery and sensors. Biomarkers were considered early on as indicators when concerns about health outcomes arose, especially during the first Gulf War regarding potential exposures. In 2000, the Institute of Medicine began taking biological samples from service members prior to deployment to facilitate analysis of deployment exposures. In 2002, there was a call to collect additional biological samples post-deployment for the purposes of health assessment responses and evaluations. Even while collecting these samples, there was no real guidance on what to look at for biomarkers; however, there was a clear need to develop biological monitoring. During this push for biomarker discovery, two levels of exposure threats were separated out. These were ambient and acute exposures. Ambient exposures were low-level and long-duration, while acute were short- and high-level exposures. Separating out the risks related to these two types of exposures allowed for strategic considerations regarding operational scenarios. The idea of this not yet developed bio-monitoring capability was more finely tuned over time. Avoiding false positives, prognostic value, and assays based on credible threats were all identified as desirable criteria. Another reason bio-monitoring is the way of the future is because we know that there is a poor positive predictive value when we rely on self-reporting exposures. For instance, questionnaires and exposure history have limitations because they do not have longitudinal exposure data. Currently, there is a push to improve the DoD Serum Repository. There are some limitations that need to be addressed, including the gap between timing of blood draw and an exposure. Also, we need to look at both acute and chronic exposures and their associated health effects. Biomonitoring and far-forward diagnostics enable the detection of subclinical physiological changes in the body due to chronic, low-level exposures that may lead to serious conditions. Specific physiological systems to consider monitoring would be those that have reversible outcomes in an exposure situation. For instance, the liver can regenerate, but the CNS cannot. Other long-term health effects need to be considered as well, including reproductive health and carcinogens. Overall, no matter what specific data are collected, it must be actionable and improve our service members' health care.

Dr. Ed Perkins: Prognostic/ Diagnostic Value of Adverse Outcome Pathways

Dr. Perkins presented a novel approach on the application of adverse pathways related to exposure and impact on health. The U.S. EPA plans to develop a framework to describe the disruption of biological pathways and the resulting adverse effects. These adverse outcome pathways, or AOPs, contain a vast amount of data, with the big question being how to tie it all together. There are worldwide legislative efforts to require screening of chemicals for toxicity and link exposures to physiological responses. Due to the vast number of chemicals that exist, there needs to be a high-throughput method to accomplish this task. An exposure event requires a chemical to interact with a biological molecule, leading to cellular, organ, and eventually systemic effects. Adverse outcome pathways help to map out and link the cascading effects of chemical exposures to physiological responses. As with any method development, there are rules for developing AOPs, including that they are chemically agnostic and modular. Sometimes, different chemicals will interact with the same cellular receptor, starting the same or similar cellular response. Each key event from an AOP is a measurable unit of observation that is linked to an adverse effect, and thus could be considered "biomarkers". These biomarkers predict downstream adverse outcomes. AOPs are also linear and contain pragmatic units of development, providing measurable causal linkage to events. When two AOPs intersect, they may trigger a larger and more complex cascade, the understanding of which may lead to the development of additional predictive tools. In the context of bio-monitoring our soldiers, AOPs can link biomarkers to adverse health effects. An example of this would be the steatosis AOP network. After examining multiple measurable effects of the steatosis AOP network, it was found that you could predict, with 100% accuracy, resulting steatosis if you inhibit a single enzyme, thus positively identifying the biomarker directly from an AOP. The linear relationship of AOPs allows you to walk backwards in the pathways to logically deduce and perform calculations to make sense of the biology that is happening. This allows us to look at multiple TICs/TIMs to characterize their health impacts and develop networks associated with detectable biomarkers. Using a network that links key events to AOPs that are expert-curated builds trust in how we are linking pathways together and will add validity to biomarkers.

Dr. Camilla Mauzy: Integrated Biomarker Discovery and Biomonitoring

Dr. Mauzy's remarks touched on the challenges involved in biomarker discovery from practical experiences. Biomarkers can be used for a variety of performance-related effectors, including exposures to chemicals, fatigue, and stress. Due to the amount of chemical agents that exist, there is a push to look at biomarkers linked to specific organ damage as opposed to individual chemicals. Between 2003-2010, the evolving field of "Omics" led to a rapid expansion in biomarker discovery. What was learned from this is that biomarkers are relatively easy to discover, but extremely difficult to validate. Ideally, biomarkers should be validated using a systems biology approach before putting them on a device or assay. For each biomarker, there should be a well-characterized causal pathway analysis, not just an observation of an increase or decrease in a biological event. Additionally, biomarkers show up at different times, so there are both long-lasting and short-lived biomarkers. When defining biomonitoring, timing is a factor that needs to be considered. Sample matrix is another factor to consider that can vary depending on the biomarker for which you are looking. In 2004, a project began looking for biomarkers through the use of metabolomics, specifically a signature from a known nephrotoxin. Kim-1/NGAL was identified as a clinical predictive biomarker in urine for kidney damage. Since early recognition of kidney damage is useful, Kim-1 is a valuable example of a time-critical biomarker. There are also biomarkers that can predict cognitive performance and the effect of fatigue on your overall performance, which can be used to make strategic decisions for personnel assignments. Predictive biomarkers used in this way could allow for optimization of performance. When it comes to biomarker discovery, using an integrated "Omics" approach can help to

identify warfighter-critical biomarkers. Also, using the microbiome to look for changes and new biomarkers could be particularly useful, especially in the lungs.

Dr. Ellen K. Silbergeld: Gatekeeper and Watchman- The contribution of the microbiome to understanding exposure and response

Dr. Silbergeld followed with a presentation about exploring the microbiome and the impact on environmental toxicology and biomarker discovery. The microbiome, which can be defined as the entirety of the microbial world in a defined space, and the interactions between the microbial world and its domain, may have a role in understanding toxicology and susceptibility. The standard model for how external exposures are transferred and transformed within an organism does not currently include the microbiome, however, each point of entry and route of exposure in the human body has its own unique microbiome, which may alter the absorption of toxins or signals sent in response to a chemical's presence. Since any external exposure has to pass through a microbiome before being absorbed by the human body, the microbiome is an additional source of susceptibility that needs to be studied. If a microbiome alters an internal dose, even with just a small change, the range of different clinical implications could be large, due to the cascade effects of signaling. There are examples of environmental microbes found as part of the gut microbiome, which together with other factors, like the bacterial capability of methylating and demethylating mercury, allows for the possibility of these bacteria having a role in changing an exposure parameter or outcome. As an example, a study revealed that if mice were infected with *Helicobacter*, which causes a change in the microbiome, arsenic metabolism was also altered. More animal studies should be conducted to further determine the potential effects that the microbiome may have on absorption of environmental toxins.

4.2.3 Panel Discussion

Note: Joint Panel Discussion between Session 1 and Session 2. A series of question-answer exchanges were candidly captured.
Question: What is the response of the microbiome to toxic industrial chemicals and materials? Can the microbiome be exploited as a "gate keeper" for an early exposure warning?
- The microbiome primarily signals responses to the metabolome and the immune system. The immune system is very sensitive to even a small compositional change in the microbiome. Understanding the microbiome markers and subsequent responses could be used to feed forward into AOPs. There is also potential in utilizing the microbiome as a marker for chronic exposure, but this has not studied extensively enough to be used at this time. Even in studies, it is difficult to make generalizations or standards for exposures as there are differences arising from whether it is a susceptible population or an average population. There is a large amount of variability in susceptibility and responses based on individual factors such as current health, genetics and the microbiome

Question: Is it possible to use the microbiome offensively? Can a microbiome be established that will give someone protection as opposed to a vaccine or other prophylactic medicines?
- The microbiome is an easily manipulated area, which creates potential in changing it for advantageous purposes. Short-term protection is possible as shown in examples with methylated mercury. A further study in engineering the microbiome to be more or less efficient with methylation is planned. A useful application of microbiome alteration could be protecting a

population drinking water with a high arsenic concentration. A downside to this technique is the microbiome is fairly stable and will return back to its normal state after an unknown period of time. Before embarking on this task, the microbiome needs to be extensively studied so the effects of manipulating it are fully understood.

Question: How does one actually define exposure? How do you find exposures in the field?
- Defining exposure is very difficult. In many current studies exposure is just defined as someone who was deployed, but that is very gross and creates problems in examining the findings. There has not been enough time or resources devoted to specific studies. Moving forward standards for exposure need to be developed. Things to consider when developing standards involve the susceptibility differences between individuals and variations in exposures caused by slight location changes. The best way to counter these problems would be having an individual monitor on each service member to provide tailored information, but unfortunately this technology is far off. Individualized baselines before deployment, such as a blood spot could potentially be useful. The issue is also complicated by an inability to distinguish specific exposures on the ground; most exposures are unknown, which makes creating generalizations challenging. Mixtures can also have additive negative health effects that are difficult to predict. Despite the difficulties in making generalizations, commonalities need to be found as determining exposures and effects for all existing TICs and TIMs is not feasible.

Question: Have we thought about not looking at the megacity environment in a general manner, but looking at the specific megacities most likely to experience a problem requiring military intervention?
- Currently, the best studies of large cities have been in the more developed western countries, but even in studied cities it is hard to discern exactly what exposures there are. Building up a metadata database of what is allowed in each city, any known chemical plants, and information on facilities holding especially dangerous chemicals could be useful. The database will be limited by what is known and will not incorporate any of the additive effects of mixtures. A more multiplexed or systems approach solution is still needed.

Question: What organizations would be responsible for taking diagnostics for TICs and TIMs to the FDA?
- This is unknown. There needs to be a good example that it is feasible and is worth the science and technology investment before any organization undertakes the task as it would require a huge financial investment.

4.3 Session 3: Personalized Medicine Solutions for Environmental Health and Protection

Note: The following information is presented as abstracts from the various SME presentations

4.3.1 Introduction

Session chairs Dr. Christopher Bradburne and Dr. John Lewis covered current states of personalized medicine and their potential use for measuring and mitigating individualized susceptibility to environmental hazards. Personalized Medicine integrates genetics and the environment to create tailored

treatments and interventions to individuals. Generally, personalized medicine uses a systems biology approach, incorporating not just genomics, but all of the "omics". One of the challenges is integrating individual characteristics, including environmental conditions and exposome/biomarkers from an exposure event to a disease, with the purpose of managing outcomes. A systems biology approach can inform individual susceptibility to environmental and occupational hazards. Whole-genome sequencing can be used as a baseline for health and incorporated into medical records. Today, genomic information is used for guiding the treatment of cancers. Epigenetics can uncover environmental disease risk, as well as identify highly actionable performance markers. Personalized medicine has significant potential to impact the state of medical care. The principal delay for the integration of personalized medicine into mainstream medicine is the length of time it takes to tie variations among individuals to disease, and how to properly and usefully employ that information. If today's physicians adopt a personalized medicine approach, doctors will have data-driven guidance for the prescription of pharmaceuticals to their patients by having access to information on a patient's ability to metabolize certain drugs, leading to more effective drug selection and dosing. Importantly, the same genes responsible for metabolizing drugs, cytochrome P450s, are responsible for metabolizing environmental xenobiotics. Different genotypes vary by ethnicity and sex, and could provide an important start in the search for individual susceptibility to environmental toxicants. There are multiple challenges that personalized medicine faces in both the civilian and military arenas, including analytical validity, clinical utility, and legal/social implications. While civilians are protected under the Genetic Information Act (GINA), military members are not. Regardless, there is still a long way to go in tying genetic variants to genotypes. Recent advances in long-read-sequencing technology have helped provide more accurate information on variants, including structural variations and single nucleotide polymorphism (SNPs) to inform on disease onset. Another huge challenge that faces personalized medicine is the education gap in both the military and civilian arenas. In 2010, the Air Force investigated personalized medicine potential by recruiting individuals, SNP chipping them, and then surveying risk factors from the individuals. The idea was to ascertain the clinical utility, in context of military population, as well as educate providers who could see both risk factors and genetic information. Medical doctors need to be able to understand genetic information, in order to make informed treatment strategy decisions based on these data.

4.3.2 Presentations

Ms. Carrie Blout: The Medseq Project

Ms. Blout presented research findings from the Medseq project and the issues regarding genetic information and its utility. The rise of personalized medicine has created not only vast amounts of possibilities for treatments, diagnostics, and other medical applications, but it has created many questions on how to move forward. Some prevalent problems are related to information security, incidental findings, and how many doctors are inadequately prepared to understand and convey genetic information to patients. Also, before investing in personalized medicine, many want to understand its actual clinical utility or if there is a preventative measure or treatment that can actually be taken as a result of the personalized medicine information. The MedSeq Project, a randomized study with a diseased population and a control population of unaffected individuals, aims to study the medical, behavioral, and economic outcomes of whole-genome sequencing for personalized medicine applications by following both doctor and patient outcomes. In regards to clinical utility in this study, there were laboratory tests, referrals, and even medication changes made as a result of the genome sequencing. Also, genetic counselors reviewed physicians' reports to their patients to determine the accuracy and error rate of the information conveyed, finding that there were no high-risk errors, which is a misinterpretation of genetic information utilized in the study. However, 4 medium-risk errors and 22 low-risk errors or omissions were made. Cost analysis

between the genome sequencing group and the non-sequencing group revealed a differential cost of $7,229. Additionally, psychological impacts and concerns on information security were gathered from the participants. Findings showed there was no significant difference in the psychological state of the control group and the group who had their genome sequenced, and that 66% percent of study participants were completely comfortable with genetic information being placed in a standard medical record. The next steps involve conducting further studies and determining long-term benefits associated with personalized medicine.

Dr. David Valle: Individualized Medicine in the Genomic Era

Dr. Valle introduced the concept of "individualized medicine" and the implications of genetic and environmental variations on human physiology. The term individualized medicine, used to ensure understanding that the medicine is for one particular individual, and not just based on a personal relationship with a doctor, has been brought on by the evolution of genome sequencing and sequencing technology. Individualized medicine aims to identify variations that inhibit individuals from maintaining normal physiology. To complicate this, there are not only unique genetic variations, but each individual also has its unique environmental exposure history, which impacts susceptibility and subsequent health effects; this leads to individuals experiencing the same exposure but having different reactions. Wearable, individualized nano-devices, which have been customized with genetic information and past environmental exposures, could be utilized to measure current exposures and real-time physiological data. This technology, and the informatics capability to handle these "big" data, do not currently exist and should be considered as a possible solution towards which we must innovate.

Dr. David Graham: Personalized (Precision) Medicine in a Real World Environment

Dr. Graham showed findings from his research and the interest in deployable solutions for sampling (sample-prep) that allows multiple tests done from one stored sample, and the impact of having bio-repositories. He also presented information on newly developed technology to assist in this effort. There are many useful pieces of infrastructure to analyze metabolomics, lipidomics and other "omics", but they are immobile and in some cases require extensive modeling. There is much interest in turning these capabilities for detection into a more deployable, bio-repository-based solution. Two studies were examined in regards to this goal; the first related to HIV neurological disease, the second related to cardiovascular disease. In the neurological HIV disease study, a predictive biomarker for brain inflammation was found in non-human primates (NHPs). The findings will be applied to bio-banked samples by using a mass spectrometry-based analysis for proteomics, metabolomics, and lipidomics. A new sample preparation method, which allows for multiple analyses (proteomics, metabolomics and lipidomics) to be done on the same sample, reduces the variability between the measurements. In the heart study, a metabolite's distribution throughout the heart was examined. The aim is to learn from the distribution model and reach out to bio-banks to test their samples. There are new, validated technologies that may assist in this effort, including a sample preparation that can isolate cells from plasma, a kit that contains chemistries to quench metabolism, preservation of a plasma sample at room temperature using the "'omics" technologies that were mentioned above. Additionally, these technologies are now being applied to the measurement of chemotherapeutic drugs in human saliva. Future work will be done in implementing targeted, high-sensitivity assays for multiple chemistries.

4.3.3 Panel Discussion

Note: Panelists were speaker participants on Session 3. A series of question-answer exchanges were candidly captured.

Comment: Civilians often have a misconception about what can be done in a research environment for the military, which is often very mission-focused. Attempts to use wearables in the past have only been partially successful. It's difficult to get a soldier to wear sensors properly. Additionally, there is an issue of receiving true informed consent from a soldier because they are vulnerable population. Perhaps it would be better to grow monitoring technology outside the military and then bring it in. Another thing to consider is that genetic counselors are great at describing the odds based on genetic information and military leaders are great at making decisions, but they do not know how to make informed decisions based genetic data.

Question: Given asymmetrical warfare, are we doing ourselves a disservice by not investigating genetic optimization capabilities when our enemies might be honing their forces there?
- CRISPR technology enables us to change SNPs or genes, ultimately inserting or removing certain traits. There are a lot of ethical considerations surrounding this capability. A survey captured thoughts and feelings about genetic manipulation using two different scenarios. The first scenario asked people if they were ok with genetic manipulation to improve the outcome of someone with muscular dystrophy and there was almost a unanimous yes. However, when this same group was asked about using genetic manipulation to improve intelligence, only 10% said yes.
- Given there is no "one" gene that can be modified to make a superior warrior; there are ways to use genetic data to identify susceptibilities relevant to the military. For instance, PTSD in influenced both by experience and genetic makeup. The military has experienced tremendous losses of people they invested in who went on to develop PTSD. Although looking at the genotype is great for patient care purposes, unlike the genotype, the phenotype can be observed with certainty and change.

Question: What tools and methods for personalized medicine are available today that can be implemented in regards to being actionable, achievable, and foundational?

- The field of personalized medicine still has a long way to go before it can be very actionable. Our metabolism produces a broad range of molecules and there is no one method that could measure everything. Due to the complex nature of personalized medicine, we need a test that can look at everything using many methods and chemistry. This sort of effort requires many very smart people from different fields, working together to address this issue. Perhaps a centralized biobank that stores both DNA and RNA can be sent to world experts. As for the environmental component to personalized medicine, that is even more complex and difficult to study. Even though the battlefield is not an easy place for environmental research, it should be of great concern to the military. For instance, military service members go through very stressful training and it would be a good group to look for effects of stress on the metabolism and how it is influenced by genetics.
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4.4 Rotating Working Group Discussions

4.4.1 Scenario Summary

The working group discussions were facilitated by subject matter experts introducing a realistic life-event scenario. The scenario narrative was as follows:

An Army Quartermaster platoon is deployed as part of a larger CJTF in response to a major earthquake in an ally's megacity. The damage to the infrastructure is extreme with many displaced people and unstable structures.

The unit is forced to set up operations and quarter near the airfield within an industrial park in order to conduct their mission and to stay out of the areas where displaced civilians are now living in tents. Stable buildings are scarce, so the unit inhabits the first one they find that appears stable. It has space for their logistical operations and a sleeping area. However, there is no running water in the building and or power. As such, a field latrine is built near the loading dock area of the building. In addition, the cellular service is out in the area, so the only communication source is a tactical radio.

The structure is a 2 story warehouse for what seems to have been a nearby manufacturing plant and adjacent taller plant collapsed in the earthquake. There are many containers, boxes, buckets, and barrels of supplies stored in the same area where the Soldiers are quartered and additional containers are stored upstairs. Some are marked in what appears to be Chinese or possibly Hangul. There are many boxes marked CAS# 1330-20-7 (__xylene__) and Cleanite (__TCE__), but most are unmarked or marked in a way the personnel does not understand. A young soldier opens one of the jars from a box marked with 2831 (__1,1,1-Tetrachloroethane__) a red square. The soldier reacts strongly after smelling the substance, resulting in the jar falling to the floor and shattering. A minor attempt to clean up the spill occurs, which contains some of the substance, while the remainder evaporates or seeps into a crack near the wall. The Soldier complains of the smell remaining in his nose for an extended period of time, as well as watery eyes. However, the soldier seems fine after an hour or so.

There is also a small pool of a thick liquid at the entrance to the building, which is walked through as the personnel come and go. The mechanic in the platoon thinks it smells like anti-freeze, but no one thinks much more of it.

The 2LT and medic attached to the platoon have concerns about the building's contents and odor. However, there is not another option to setup operation and   they expect to stay for only few weeks. The Soldiers set up their cots in the rear of the warehouse open area, so that their 24hr operations can be run from the front of the warehouse near the loading docks. Some comment about the odor in the sleeping area, which has little ventilation. However, their options are limited, so they continue their mission operating/sleeping in the warehouse for most of each day and night, with the exception of limited disruptions consisting of outdoor exercise and smoke breaks.

Bottled water is currently plentiful for the unit. However, sanitation and hand washing is a challenge. They have hand sanitizer, which most are using prior to eating.

On week 13 of their deployment, the white male junior enlisted Soldier was found unconscious near the side of the building. Near him was a bottle of the same substance he dropped earlier on the deployment after sniffing from it. He is evacuated to the CJTF's medical company on the other side of the airfield.

Ground movement is difficult as many roads are still not entirely cleared and the massive population of the city creates significant delays as they also are trying to restart their routines.
After a short investigation, it is found that the junior enlisted soldier and at least 2 others have been huffing from jars found in the warehouse when not working.

Week 18, the rainy season starts. The seemingly good roof is shown to be in poor condition as water starts to fall in many locations throughout their workspace and sleeping quarters. The LT again requests to be moved, but there are still no better options and the rain has made ground movement more difficult. The displaced civilians are no longer patient and have begun moving into damaged structures to get out of their tents and the muddy fields, which makes a move even tougher. After a few days of rain, a small section of the ceiling gives way and buckets of foul smelling water with an oily sheen douses one of the sleeping females completely. She awakes and quickly starts to complain of irritated eyes, nose, and throat. Others in the unit calm her down because they realize she is in need of medical attention. They then start to strip her down and douse her with bottled water the best they can. She is then wrapped in a clean sleeping bag and taken by ground (slowly) to the medical company and while en route, she starts to complain of a headache and appears drowsy.

Her injury and the damaged roof prompt the HQ to move the platoon the next morning. The building collapses three days later due to the continued rain.

The scenario was used to prompt thoughtful discussion on the challenges related to the development of health risk assessment and environmental surveillance tools in the Megacity OE. The SMEs arranged for question-guided discussion, however, given the enriched diversity of the group, numerous topics emerged, and some are not in particular alignment with a workshop session. The notes compiled below are thoughts/topics captured as conversations evolved.

4.4.2 RED Team General Discussion

Note: Although there were pre-outlined questions based on the various topics, not all discussions among the groups adhere strictly to those guidelines. These notes were captured <u>candidly</u> from exchanges among participants.

Question: What are the current pre-deployment capabilities? What would we like to know going into this situation (the earthquake scenario)?
  - There needs to be a lot of additional intelligence before entrance. Knowing of any other issues caused by the earthquake, such as fires or water contamination would be very valuable. Additionally, knowing information about the specific area is pertinent. Information on the climate, endemic pathogens in the area and typical chemical industries can help in selecting gear, issuing prophylactics or vaccines and determining what chemical exposures to look out for. Details about the specific service members on the mission are also relevant. Are there any members of the group who are especially susceptible to anything? Are there women of childbearing age? Problems can arise when looking at susceptibility, as some troops may not be able to function if their female members could not participate, due to potential exposure that could cause reproductive harm. It could also be seen as a policy issue of limiting experience and subsequent promotion opportunities based on gender.

Question: What actions should be taken for soldiers pre-deployment?

- A baseline needs to be taken. There is data from Iran/Iraq about mustard gas markers found later in Iranian soldiers, with serum and saliva samples being used to see what the exposure was. These kinds of immune markers have potential for being a good baseline. Additionally, a physiological and hearing baseline should be completed pre-deployment because currently they are only being completed post-deployment, making it difficult to determine change. Also, any nutritional, vaccine, or prophylactic medicine concerns should be addressed at this time.

Question: What is the best method for establishing a baseline?

- Baselines are crucial because evidence upon return is reduced if there is nothing to compare it to and determine the change. Difficulties arise, as it is hard to know what to measure beforehand if there is no information on the potential exposures of deployment. However, bio-banking the samples until a later date can solve this problem. Bio-banking will also allow for samples to be looked at later date for genetic and epigenetic information. Every soldier should have a baseline taken pre-deployment and post-deployment, then biomarkers can be examined and differences quantified.

Question: What are actions we can currently take for an area with unknown chemicals?

- This is where having a wearable, providing information on what someone was exposed to, would be extremely useful. More physical testing before and after, or a biomarker that could help determine exposure after the fact, are other options.
- In the attempt to identify the unknown chemicals, there needs to be an application where a soldier can enter in any identifying information, such as a CAS number, and get the chemical information in English. This needs to be on a phone that can be used without Internet or connectivity.

Question: What gets entered into this troop's medical records post-mission?
- It is ideal to find out the chemicals in the location and enter the exposure into their narrative in the medical history. This information needs to get to the medical provider post-deployment. Complications are caused by the inability to go back and take samples in some cases. Looking at biomarkers or immune responses could help determine exposures, but mixtures of chemicals and exposures could complicate this.

Question: What can we do about people in the same troop experiencing different exposures and different amount of exposures? (50% of the troop out on convoy missions in the scenario)
- It may not be possible to do anything about this. Rotating people through the positions is the obvious answer on "evening out" the exposures, but people are trained for specific jobs. Personal monitoring would help track the exposure of each person.

Question: What are the current gaps in the technology?

- There is a gap at the environmental sensor level. We need a sensor that provides interpretable actionable information about the environment. There is also a gap at the personal dosimeter, which would ideally be able to detect more than one thing and indicate if a soldier has been exposed.

Question: Would it help for troops to be able to identify chemicals in the area? Should this technology be far forward or just at the leadership level?
- Opinion 1: If it was an electronic capability that did not add a lot of weight, it could be helpful in every soldier's hands.
- Opinion 2: It should not be in every soldier's hands. If the information provided is actionable and there is modifiable behavior, the decision will need to be made by leadership. It is also important to consider that the leadership will make a decision to proceed with a mission, even with the knowledge that there may be risk of exposure. Studies to test how well new methods work are also hindered by the commanders focus on helping their soldiers now and completing the mission at hand, making them less likely to do anything requiring work now if it only helps in the future.

Topic: Thoughts on AOPs?
- There are many thoughts on whether AOPs are the best methods of tackling this problem. Concerns come from the fact AOPs do not actually detail what the exposure is; that will need to come from a personal monitor or detector. Supporters think the actual exposure is not the most important part, as the treatment is the same for many different exposures. Problems with this approach can arise when an individual's past exposures, past history, and genetics affect the response to an exposure, creating a path that could not be predicted.
- AOPs need to be actionable. The first step in AOP creation is going from an environmental exposure to a personal exposure, and then to the actual physiological effect. The beginning of the AOP is a critical monitoring point, as it is the point where intervention is possible.

Topic: Thoughts on sampling?
- Thought needs to be put in what the best kind of sample to gather information on the environment is and how will it be analyzed. Also, it needs to be determined who will be completing this sampling. Should there be sampling capabilities in the hands of every small group, even if they do not have a lot of support? Or should the sampling be the responsibility of a separate environmental team? A protocol should be established; maybe a team is required to take a sampling device if there is concern about exposure and have them be responsible for bringing a sample back for analysis.
- It may be helpful to start sample collections now preemptively in areas that we expect to have to enter in the future. UAV's could potentially be utilized in unmanned sample collection if more work goes into customizing them and reducing the technology gaps needed for this function.
- For soldiers sampling to determine exposure, in addition to samples pre- and post-deployment, there should be samples taken at time points in between. Blood spots have high potential, as they do not need cold storage and can be done by soldiers themselves. Blood spots could be genetically and epigenetically analyzed at a later date. There is currently an epigenetic signature for smoking; can this methodology be transferred to other chemicals or exposures?

Topic: Thoughts on intelligence and information?

- Intel is key in any mission and is needed before entry. We need to start collecting information when we realize there is going to be a potential megacity problem. Theoretically, we should be able to take intelligence and use informatics to generate a list of potentials of which we should be aware.
- Outside sources, like National Center for Medical Intelligence, have information. If the military could prioritize locations of interest, they might be able to leverage their information.

HUGE TAKEAWAY: Information is useless unless it is actionable. Commanders need to be able to make decisions based off of information given by any exposure or diagnostic information.

Question: What research areas show the most promise in determining susceptibility? How does emerging research compare to classically-determined risk factors? Can susceptibility even be used?

- AOPs represent a research area that shows promise in personalized medicine, even though they are not ready yet. Drawing a line from an exposure to physiological condition is the main objective of AOPs, and further down the line, we will become more confident in the physical outcome. Eventually, they could provide information on how to intervene on the pathway, or inform surveillance that needs to occur on individuals.
- There is currently not enough research on epigenetics to cast it as a front-runner in determining susceptibility.
- If a list of genetic markers that indicate susceptibility to agents, whether chemical, TICs, or TIMs has been established, it could be very beneficial. This project is starting to be worked on, but it is still difficult to phenotype. Additionally, the downside with genetics is that it is very variable and anything seen on the genetic level can result in significantly different physical outcomes.
- If the metabolic or degradation pathways for the chemicals of concern were known, the enzymes involved could be looked at genetically to determine if there are any factors affecting the metabolism and subsequent susceptibility. This is a similar approach to how cytochrome P450s affect how drugs are metabolized. There would need to be a way to group chemicals because going through every TIC or TIM is just not feasible.

Question: Biomarkers have been used in animal studies to correlate a marker to a physiological effect with a relatively high degree of confidence, but is there a return on investment on these kinds of studies? Is it possible to reduce the effects or is it just for knowledge and detection?
- This comes down to cost feasibility. Even if we know the mechanism, it may be hard to develop a drug for that due to funding. A more generic intervention, such as an aspirin regimen in the cardiac biomarker example, or increased surveillance, might be more feasible.

Topic: Would commanders even use this information about susceptibility and other personalized medicine topics? Would they remove someone from the group, reducing their agility and ability because of a susceptibility to a potential exposure? What level commander gets to make these decisions?
- Combat commander will make the decisions. Keeping the team together maximizes the group potential and commanders are willing to accept some risk, so there needs to be very strong scientific evidence for them to alter their plans. It is important to advise them the best we can and when science gets to the point we can determine high susceptibility, we need to make sure they

understand the potential adverse outcomes. Despite advising the scientific community, the combat commander will still make the decision about the requirements for entry into an operation and the best we can do is advise them so they understand the risk. There are ethical concerns of removing soldiers from a mission based off of a potential susceptibility marker. It might be a better approach to accept that exposures will occur and coming up with solutions to determine what exposures might occur and how to minimize the adverse effects.

Topic: Thoughts on personal dosimeters?
- A personal dosimeter that could be placed on a soldier without hindering any mission functionality is a good idea. Ideally, it would be similar to a radiation dosimeter, but having 80,000 TICs/TIMs complicates this option. Also, difficulties arise in correlating dosimeter readings with an actual psychological effect. A monitor that focuses on measuring and monitoring the psychological signs of stress is also being considered.

Question: Is there an option of setting up a database of usual medical effects and exposures to troops in unique situations, and an ability to follow them down the road to see if there are any effects?
- A project right now is starting to link exposure to health records. It would help tie exposures to physiological effects and could aid in the identification of cohorts for studies. Current electronic health records are not quite capable of this right now.

Question: In a particular setting with known probable chemicals, can the situation be linked with AOPs and eventual outcomes, and automatically generate a one-page report on concerning chemicals, PPE needed, and necessary interventions.
- A similar system is currently being developed. The idea is to put it on a phone and provide intelligence information about relevant chemicals. If this system can provide an actionable item, a correlation between the chemicals in the location and what the actions are to do, it may increase compliance and interventions taken in the field.

Topic: Other random thoughts.
- Could soldiers in the field periodically take blood spots?
  o Yes, it would be fairly easy, but it would not be helpful in quantifying the amount of exposure due to the methodology of blood spotting.
- Is technology anywhere close to being able to have a handheld detector to wave around and identify any chemicals in the air?
  o No. This technology does not exist and is complicated by the vast number of possibilities of chemicals that can be found in the air.
- Have any good studies been done on pesticide susceptibility?
  o There have been animal studies and some clinical studies on humans with occupational exposure, but there currently are no personalized medicine or GWAS studies on this topic.

4.4.3 BLUE Team Discussion

Note: Although there were questions based on topics pre-outlined, not all discussions among the groups adhere strictly to those guidelines. These notes were captured <u>candidly</u> from participants

Question: Regarding Megacities as OEs, what pre-deployment capabilities and diagnostics are ideal?

- Ideal pre-deployment preparedness would include environmental intelligence (however it is collected) describing facilities in the area and what the hazards are. For this environmental data gathering, drones could be used. However, there is also a need for pre-deployment diagnostics and monitors for the individual soldier. We currently do not know how to customize medicine or establish a baseline for individuals. An idea would be at minimum to collect a blood sample, saliva, and microbiome pre-deployment. Collecting these data pre-deployment hopefully will provide some sort of diagnostic baseline in the event of an exposure. However, what about highly toxic chemicals that produce the same medical distress across all individuals? In these cases, you do not really need a baseline clinical assessment. Where the baseline assessment is really necessary is with less toxic chemicals over long periods of exposure that produce subclinical symptoms. An example of this would be pesticides.

Question: In regards to geographical data, how do we synchronize these data with a potential exposure threat to make it actionable? How do we disseminate information regarding threat exposures?

- Perhaps using a tool, such as Google maps, we could direct people where not to go, based on collected geographical threat data. Additionally, there is a critical need for educational tools that disseminate information to all levels in the military regarding environmental health hazards. This information could be incorporated in leadership training as well as the medical profession. In the civilian world, there are courses available that focus on subjects, such as toxicology, biomarkers, and genetics. The question becomes, how are they organized and how can they be focused to benefit real-life scenarios in the military? How do we incorporate appropriate pre-deployment training and tools to the environmental health officers and the individual soldiers?
- A field-ready idea would be to develop an application that could provide instructions on how to handle a HAZMAT situation using situational data input. This would require a database that could possibly cause classification issues and not everyone would have the clearance to access the data. A potential solution to this is to make sure the data are at the level of useable, accessible, and actionable information. One gap that should be considered is that all 80,000 chemicals may not be known, but their combinations and the consequences thereof are not known.

Question: How do we address the problems of unknown chemical mixtures? What about chemical sampling? How can we collect samples post-exposure events?

- It is clear that there is not enough knowledge for sampling chemicals during exposure events. Having soldiers collect samples on the fly, with no knowledge about the chemical, and how to safely store it to prevent safety issues. One solution would be to develop a sampling device that is simple, convenient, and robust, like a piece of litmus paper. Another thing to consider is where this sample can be analyzed. There is an Army lab that is deployable for JTF situations with some of these capabilities.

Question: Another consideration that needs to be made is what to put in individuals' health records, if at all, and how do you support it?

- The current goal of the Department of Defense is to collect these longitudinal health records from personal monitoring data to determine if an exposure event has occurred. Eventually, that service member would go through a clinic and those data would link up with their health records.
- Very often, exposures happen in theatre, the soldier is seen, treated, and returned to duty. Many times the records taken during these encounters are on paper and get lost in re-deployment. So, electronically capturing these events, in order to avoid loss of these records, is a main focus for the DoD.

Question: What would we like to know about the soldier before the exposure?

- The U.S. military uses a system informing deployment status by categorizing service members as individually medically ready (IMR) green, which means deployable, or red, which means deployment limited. One of the measures taken to determine a soldiers IMR status is a questionnaire. Generally, soldiers get pre- and post- deployment questionnaires, as well as a 6-month follow-up questionnaire. There is a need to collect baseline genomic data, as well as biomarker data, pre- and post-deployment. Ideally, a handheld device would be developed to self-monitor an individual in varying scenarios, in real-time, and for a particular period of time, in order to establish a baseline for that individual.

Question: How can we use biomarkers and make them an objective, actionable item for not just determining deployment eligibility, but also for identifying pre- and post-exposure events? Additionally, what specifically do we need to collect from the soldier to make assessments and establish a pre-deployment baseline?

- Currently, a device is being developed to test dried blood spots and analyze metabolism pathways, as well as lipid signaling. As the development progresses, there is room to expand into clinical chemistry assays. This device is ideal because it is stable enough to run different types of assays that collect useful archival data and it is field ready.

Question: What are the major threats in a megacity environment?

- About 80% of the pre-existing hazards in a megacity environment should be relatively predictable, leaving about 20% requiring some Intel gathering. Currently, the military tends to react instead of being proactive during missions. The goal is to learn from experience and apply what we learn to future scenarios. For megacities, the most common threat would be burns caused by implosion or explosion, producing heat. This increases chances for chemical exposure, fire, blast risks, and it creates a need for air monitoring. Other things to consider about megacities in underdeveloped countries are the potential for buildings with lead-based paint and other hazards related to outdated infrastructure.

Question: What needs to be done in order to determine which biomarkers need to be pursued?

- The Department of Defense would like to collect enough data to definitively be able to link exposure events to disease and/or injuries. In order to do so, a baseline is needed to identify a change in the soldier, post-deployment, for issues that are not genetically linked. Assessing the

individual soldier pre- and post-deployment is essential for establishing baselines, and improvements need to be made for OEH equipment and sampling.

Question: How can personalized medicine (PM) help steer the issue of susceptibility and exposures?

- When we identify susceptibilities using PM, where do we draw the line using that indicator as a reason not to deploy?
- When it comes to using personalized medicine to identify susceptibilities, these susceptibilities or indicators need to be assigned a risk level that is appropriate to the circumstances. For instance, in the case of heat injuries, some soldiers have known susceptibilities, but this does not necessarily disqualify them from deployment. However, for pilots, who have identified as susceptible to sudden cardiac death, the risk level is too high to allow for deployment. These are two examples of how circumstances may affect risk level. There are also legal and ethical considerations linked to detecting susceptibilities and making decisions based on them. Ideally, we can use susceptibility detection to prevent serious exposure events and consequences. For example, in the case of asthma, two healthy individuals may be exposed to the same hazards, while only one may develop asthma because they had a known susceptibility.

Question: What, and how many, types of susceptibilities are there? What are their associated thresholds?

- The Army is focused on sending the right people prepared for success to each mission. If they are able to identify genetically predisposed susceptibilities that might put the soldier at risk, they may decide against deploying that soldier. However, genetics does not necessarily predetermine a person's performance by itself. For instance, in the case of PTSD, different ethnicities are affected differently. From an alternate perspective, we can work on identifying resiliencies in people who are at risk for exposure, in order to prepare them better.

Question: What are the challenges facing the use and the identification of susceptibility to toxic chemicals?

- The amount of data collected on the effects of toxic chemicals on humans is relatively small, largely due to the fact that the data are collected from unintended catastrophic events that do not often happen. For instance, when looking at a Megacity OE, one way to measure the effects of toxic chemical exposure would be to look at the people who die and the people who do not. It would be ideal to use an animal model to look at the effects of chemical exposure, but they do not make great models that translate into predictive human responses because of their fairly homogenous populations. How do we use preventive medicine to get better at treating people? Since identifying susceptibility may not play the most important role, what are other ways preventive medicine will allow us to improve treatment of injured or exposed troops? One way preventative medicine can be used is to utilize identified susceptibility to guide intervention and treatment.

Question: Can wearable, real-time monitoring devices identify hazards more quickly to help prevent exposures? What about acute verses chronic exposures?

- Bio-accumulation from chronic, low-level exposure is a concern because there may be subclinical symptoms that eventually lead to disease over the long-term, such as cancer. Acute exposures to TICs and TIMs are a lot easier to treat because the symptoms onset is immediate and the treatments are usually the same across all populations. In the event of long-term, low-level exposure, patterns, such as biomarkers and any changes from a personal baseline, might help intervene before long-

term chronic issues can occur. Digital medicine, including wearable gadgets like Fitbits, are great examples of how to monitor a person's baseline and identify any changes over time. However, there are limits as to what these gadgets monitor.

Question: What can personalizing medicine do for individual soldiers? Could it empower soldiers to take more interest in their own health and therefore preventing exposure? Could this empower them before the need for treatment after an exposure event?

- In today's world, events become national news because of cell phones recording events from individual experiences. Policies are being based on these small groups of individuals who report similar experiences. Ideally, we want individual monitoring that is real-time collection, archival, and accumulative over an average 8-hour period. Biological monitoring can prevent a crisis, for instance detecting a pattern of sleep disturbance may signal PTSD development. These wearable monitors could be used to alert a person to seek treatment before a crisis.

Question: What is the major roadblock for personalized medicine? What is the general strategy, and where are we going with it?

- Precision or personalized medicine seems to be the trend and direction in which the health world is going. The Department of Defense has expressed interest in taking part in it. However, there are real gaps that need to be addressed, including capability gaps, such as real-time monitoring, resourcing, and expense gaps. Other things to consider are data management, collection, and assessment to make all of it actionable. Once we have the data that we are seeking, the question becomes what are we going to do with them. There are certain things that need to be considered, including stigma leading to reluctance to report true personal data, in order to avoid consequences. This is especially true in the military, particularly regarding mental health. The hope is that a wearable device will diminish some data biases created by the stigma. Most people are amenable to learning their susceptibilities through genomic information, but they are more concerned about how the data will be handled and if it will affect them.

Question: What new considerations should be given in the evolution of Force Health Protection Plan to longitudinally monitor exposures to TICs and TIMs?

- Regarding the Individual Environmental Exposure monitoring, there is currently a general focus on all hazards. There is a question on how to prioritize certain exposure threats, depending on the frequency and magnitude relative to location. Megacity environment exposures are basically predictable, for instance burn pits. However, there is a need for rapid fielding and there are requirements for this type of equipment in CONOPS Environments.
- Choosing the suite of chemicals to focus on while developing this monitoring equipment is the challenge. Currently, there is no concept of operations that will guide the selection of chemicals on which to focus. One idea would be to place a monitor on military vehicles to collect data on the surrounding area. However, monitoring can be expensive, both for the equipment and the data analysis. There are also passive fence line monitors that can be hung on a fence and broadcast what data it collects. All this being said, the bottom line is that we need to first identify what we are looking for before we can focus on devices that will identify it. A list generated using an algorithm identified 30 chemicals that are likely the highest risks for TIC/TIM exposure. This list can be refined and adjusted using data from existing repositories about existing risks in certain areas.

Ultimately, a high-level determination needs to be made about which chemical threats to focus on in different megacities.

4.4.4 GREEN Team Discussion

Note: Although there were questions based on topics pre-outlined, not all discussions among the groups adhere strictly to those guidelines. These notes were captured underlined candidly from participants

Question: What is the best method for establishing a baseline and monitoring the individual soldier?

- In order to establish a baseline for individual soldiers, it is important to determine how we will be collecting these data. There is currently a technology that uses blood spots that may have the potential to be tailored to collect data for biomarker detection and characterizing adverse outcome pathways (AOP's). There is a focus on longitudinal tracking of data, which would require a device, such as this blood spotting technology, to be stable and mobile, so that the soldier can carry it with them. Serum or blood is not always the ideal type of sample to collect, and therefore other options should be considered, including saliva.

Question: How can we use susceptibility data to empower the individual soldier and how do we monitor the environment for potential hazards that could affect those susceptible individuals?

- One of the reasons for monitoring and collecting medical data from individual soldiers is to identify individual susceptibilities, so we can make informed decisions about protection and prevention for possible exposure events. Susceptibility data and environmental surveillance go hand in hand when it comes to protecting the soldier. Potential methods to monitor the environment can include wearables or chipped weapons with digital recognition that could query store databases while providing geographical coordinates of the individual. Ideally, the databases would house information about potential exposure threats according to the location and provide instructions on how to handle potential exposures.

Significant Takeaway: There is a need for wearable detector technology that incorporates biomarkers and AOPs. When it comes to protecting the soldier and preventing exposure, the mission takes priority and any technology developed exposure prevention cannot impede the mission. Another important thing to consider in the development of detection technology is to engage the end user to refine what is needed and will be used.

Question: What is the current technology for assessing and monitoring chemical threats? If you could take a clinical test, what would it be?
- Early markers of injury in general and especially early markers of specific organ injuries are of high interest to ER physicians. Problems arise from knowing the exposure in the field and actually validating it is causing the health effects to both the whole body and organs. To be able to use biomarkers for medical purposes, patients need to be looked at for prognosis, rather than just surveillance from an exposure, and there needs to be a clear linkage to the medical outcome.

Question: Concerns related to megacities?

- The general concern is how the exposure to the megacity environment will affect long-term health of the soldiers. Commanders may see the operation as fine, as there is only low-level exposure expected, but at this point, the health effects are still unknown. Studies have shown people in megacities have been dying ten years earlier, so concerns about long-term health effects have validity. One specific concern is the increased levels of carbon dioxide and noise, which may cause damage to ear cilia, and respiratory problems caused by pollution particulates.

Topic: Thoughts on susceptibility?
- Susceptibility is important because in these environments, it is typically a constant exposure to a low dose. It is also important to start looking into the differences between catastrophic site exposure and prolonged long-term exposure. The chemical exposure intake, combined with the genetic makeup of an individual, is what causes the individual's specific response. For example, it is possible for two soldiers to drink water from the same location and only have one get sick. If the scientific community can tie genes to exposure effects in people, would it be possible to make choices based on the location and suspected exposures to determine which soldiers should be deployed? This could also potentially be done with a biomarker. Looking at biomarkers for susceptibility would allow for keeping soldiers with low tolerance for the exposures out of the operation. All this information with susceptibility is only important if it is actionable.

Topic: Thoughts on monitoring and measuring?
- A non-invasive form of monitoring is the end goal. Thought is being put into monitoring a stress biomarker, such as cortisol. Additional monitoring of a neurocognitive performance marker, facial/voice stress, and reaction time test could be useful. Collecting this information raises concerns about information security and ramifications on military operations.
- A combined risk assessment and a cataloged blood spot are a good starting point for monitoring. This can give direction as to where we are going and how to analyze exposure over time. Also looking at "omics", exposure records and bio-repository information could be useful.
- Can the collection and monitoring be tailored to megacity environments? For example, are there susceptibility markers for asthma or other things that will be affected by the megacity environment? What are the best samples to take in order to capture these markers?

Question: What kind of actionable items can come from susceptibility detection and real-time monitoring? What are the issues surrounding these capabilities?

- When it comes to detecting susceptibility to certain chemicals, it is not feasible to cover all chemicals. There needs to be a down selection process that identifies the most likely offenders. Additionally, there are many ethical considerations when making decisions based on susceptibility data. There are wearables that currently exist, such as the Fitbit, which monitor real-time medical data, such as pulse rates. Perhaps real-time monitoring can detect small, sub-clinical changes from long-term, low-dose exposure and prevent greater consequences from developing by alerting the individual. Additionally, there is a need for handheld devices that can detect the chemical threat. Ideally, this device could link to an actionable database containing information about the chemicals it detected and how to respond.

Question: What are the particular issues surrounding personalized medicine and the data it provides?

- Personalized medicine is personal and there is a lot of stigma surrounding the issue of how to handle the information and health data. Ethics and policies need to be put in place to determine when and how this information is disseminated, as well as to whom. Personalized real-time monitoring is critical for detecting potential exposures and preventing adverse health effects. Additionally, intelligence regarding possible exposures prior to entering an area is critical for mission planning and determining risks. With regards to these monitors, there needs to be a method to gather intelligence, in order to determine for what purpose the monitors will be used.

Question: How do we identify the specific biomarkers that indicate relevant physiological changes that occur post-exposure?

- Adverse outcome pathways are the best way to identify and build a list of relevant biomarkers for exposure events.

4.4.5 Working Group Wrap Up I

Note: This is information compiled by the session chairs during the rotating working group discussions as it pertain to their lead topic.
Facilitators: CPT Blair Dancy and Mr. Steve Patterson.

During this discussion, several gaps were identified for various stages of an operation in a Megacity OE. Beginning with pre-deployment, there was a focus on both environmental monitoring and biosurveillance of the soldier. There was a specific focus for environmental monitoring on the collection of information about the environment prior to entering it. For instance, learning about the potential for fires and lack of sanitation or direct intelligence collection through drone sampling to determine potential exposures.

While discussing pre-deployment for the individual soldier, it seems there are some revisions needed for the deployment health assessment. For instance, instead of taking samples from a soldier just prior to and after deployment, there needs to be an individual longitudinal record throughout deployment. Naturally, in order to achieve this, the need for a wearable biomonitor emerged. The monitor needs to be digitized and able to capture and analyze data. In addition to the longitudinal biological sampling, there needs to be event-driven sampling, such as the blood spot technology that can target suspected toxic threats. Ideally, all data collected would be easy to archive. Another gap that was identified during the discussions was the inadequacy of the current DoD Serum Repository. For instance, there needs to be more diversity in the sample matrix, including saliva and other types of samples. The longitudinal biomonitoring should help in establishing physiological baselines for each soldier. Additionally, there needs to be an established way to determine susceptibility in vulnerable populations, and doing so prior to deployment would be ideal.

4.4.6 Working Group Wrap Up II

Note: This is information compiled by the session chairs during the rotating working group discussions as it pertain to their lead topic.
Facilitators: Dr. Daniel Ippolito and Dr. Charles Young

The discussion generated comments on how to adapt current pre/post-deployment questionnaires to more objective measures using biomarker panel assessments. An example of which is the pre-deployment collection of stress and unstressed baselines in garrison/training scenarios. During the lifecycle of the deployment, collect biomarker information and translate exposures to VA for post-deployment. Another topic brought up was related to UAVs used in pre-deployment intelligence/reconnaissance for air sampling, in order to determine the possible chemical exposures.

In terms of gaps, it was mentioned that we do not currently have a panel of assessment biomarkers and there is a need to collect and store specimens until we have the capabilities (mission issues: commanders are reluctant to perform non-mission-essential tasks). Regarding technologies, blood spot technology is advancing, and it seems it may be a possibility in the near future. There was also the mentioning of Spirometry endpoints technologies.

Other comments addressed detection. If the chemical is known, conduct direct detection; if unknown, base assessments on symptomology.

The topic of tools to identify individuals was discussed. Tools should stay in the control of healthcare providers, not soldiers. Individual commanders and/or leadership have a responsibility to prevent exposure. Another topic mentioned was the need for retaining samples of air quality and gaining reconnaissance before the deployment happens (Medical Intelligence). The question, "is medical intelligence during pre-deployment sufficient?" was posted along with, "have there been improvements to better protect deployed forces?"

Regarding sensors, the need for environmental detectors, personal dosimeters, and how they impact the identification of early steps in the AOPs that are actionable was discussed. Comments were discussed regarding the need for actionable assays and the fact that one should not conduct an assay without having an actionable treatment strategy.

Other comments addressed the use of photographs for reachback to determine what exposures occurred. How industrial hygiene exposure scenarios differ from combat situations: immediate/acute effects versus long-term, chronic, cumulative exposures.

Information about AOPs was also addressed:
- Kinetics of AOPs: using AOPs throughout the life cycle of exposure
- Need to be quantitative and actionable
- Early molecular initiating events are more likely to be medically useful
- If we have 100 top biomarkers of AOPs on a chip at $1/chip, predict pathogenesis

Additional information discussed by the group included:
- Using blood spots, chemical/sweat stress detectors: physiological monitoring that does not interfere with mission
- Younger generation is concerned with health care: ramification of physiological monitoring will appeal to next generation of soldiers
- Stress monitors: combining stress with environmental exposures can lead to long-term effects (e.g., cancer)
- Using the exposome to monitor health effects and prognosis
- Surgeon General's concerns with catastrophic vs. long-term, chronic exposure

General comment about technology:
- Technological "WIN": combining risk assessment applications and cataloging exposures via blood spot technology
- Using measurements of epigenetic markers for chemical or biological exposures (e.g., existing blood test for all viruses exposed to; epigenetic profile from smokers)

4.4.7 Working Group Wrap Up III

Note: This is information compiled by the session chairs during the rotating working group discussions as it pertain to their lead topic.
Facilitators: Dr. John Lewis and Dr. Chris Bradburne

For the personalized medicine discussions, <u>few</u> groups stayed on the scenario, but most discussed general policy, research, capability, or operational issues. However, the discussions were still productive. Several groups discussed the fact that personal monitors are needed and that they could be coupled to biomarkers. Importantly, baseline information on biomarkers tied to health effects is sorely needed. The DoD Serum Repository could be used to enable this, both for research purposes and operational requirements. You would not even need human genomics. Gaps abound though, such as the new EHR being unable to handle 'omics' or other new biomarkers. A potential issue with geo-locational use of samples submitted to the DoD Serum Repository may be the classification of deployment records.

Other important issues are the policy ones of having 'omics biomarkers pre-deployment. Does it prevent deployment? What is the threshold of risk? About how many types of susceptibilities are we thinking? Known susceptibilities are not that different from common military practice. An example is the MOS studies which initially asked 'What can women do?' when they should have been asking 'What needs to be done?' With genetics, it can be very 'fuzzy'… all-or-nothing genetics is very rare. Additionally, the other side of susceptibility needs to be thought of: For example, if you screen out the 'susceptible' groups from exposure to a hazard, then you are sending the other group into that hazard.

Wearables could be important for personalized susceptibility monitors. Would wearables like the Fitbit be able to provide 'actionable' information? Could wearables be tied together and put to work as triggers to action (avoid, take samples, etc…). An important joint project in individualized exposure monitoring is the ILER (Individualized Longitudinal Exposure Record). Even with wearables, a big part of the question is really how you monitor exposures. That is a gap. How do you develop TICs/TIMs to go after? Do you develop passive fence line monitors? Should we follow everything NCMI does for battlefields? Can we get something to drive this requirement, such as a request from a COCOM?

An important start for linking TICs/TIMs to 'omic' biomarkers is the Adverse Outcome Pathways (AOPs). Other than highly penetrant Mendelian traits, you could go after coupling TICs/TIMs into AOPs. You would need to define them and there are only 10 or so chemicals that have susceptibility associations. You would need to focus on all aspects of the science, such as bioavailability of the TIC or TIM, and even then, most of it is just 'pieces' of solid info right now. Population genetics like GWAS are not reliable. There needs to be more science and more information. Providing information for command decisions is key, but in most cases, a commander will have already made the decision. For example, most of the options available are common sense: Avoidance when possible, PPE when available, and post-exposure, episodic surveillance. Another issue is that commanders will not adopt a zero-risk mindset. In addition, they will want to keep the troops together (for example, all-or-none PPE).
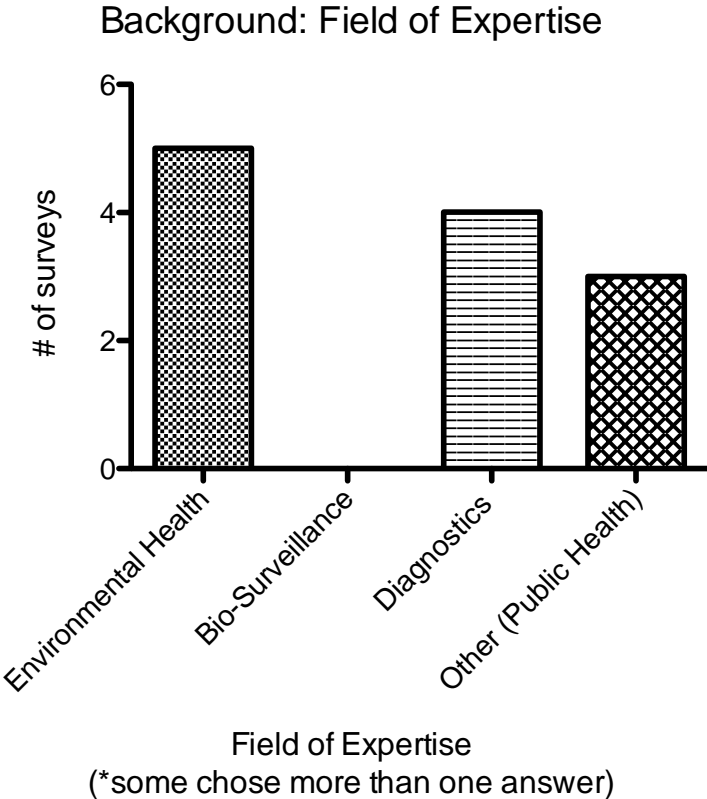
That is not to discount individual exposures monitors that could provide 'personalized,' actionable information. Personal dosimeters are what is needed for TICs/TIMs. A radiation dosimeter would be the model. A commander would likely modify duty based on dose and individual susceptibility. An important addition to this would be incorporating NCMI Intel into the equation, relating information to AOPs. Ultimately, this information could be tied together using a database of materials and nanomaterials, and the

development of an informatics tool to tie sensors, stored hazard knowledge, geolocation info, NCMI Intel, and individualized susceptibility.
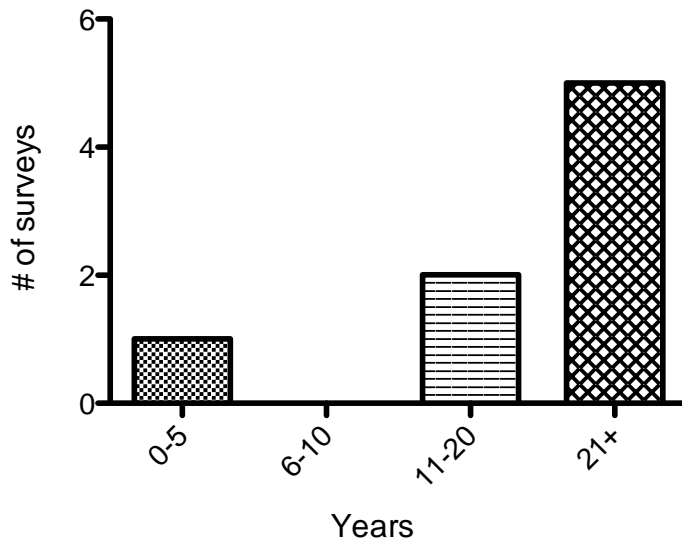
5. SURVEY

JHU/APL and USACEHR recruited a large number of stakeholder participants representing a range of experts in the field of Environmental Health. Of the 53 attendees present, 9 actively participated in completing some of the survey questions. Some of the information is presented in graphical format below.
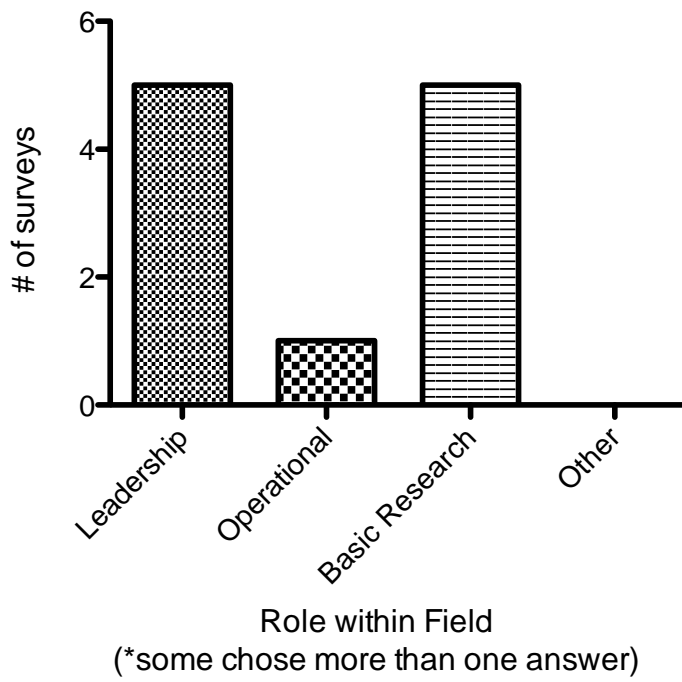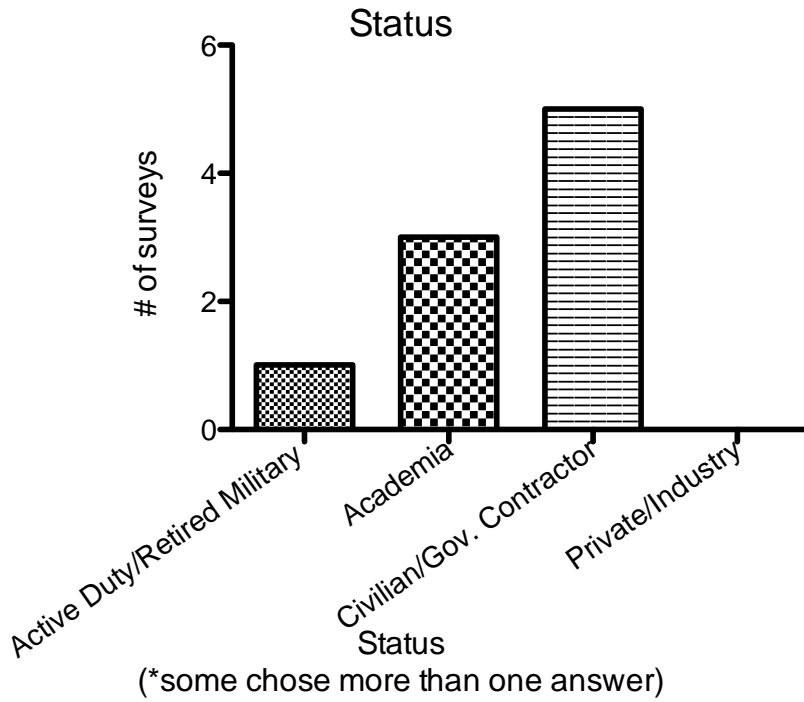
Part I: Professional Background and Demographics

Background: Field of Expertise

Field of Expertise
(*some chose more than one answer)

Experience

Roles

Role within Field
(*some chose more than one answer)

Status

# of surveys (y-axis: 0 to 6)

Categories: Active Duty/Retired Military (1), Academia (3), Civilian/Gov. Contractor (5), Private/Industry (0)

Status
(*some chose more than one answer)
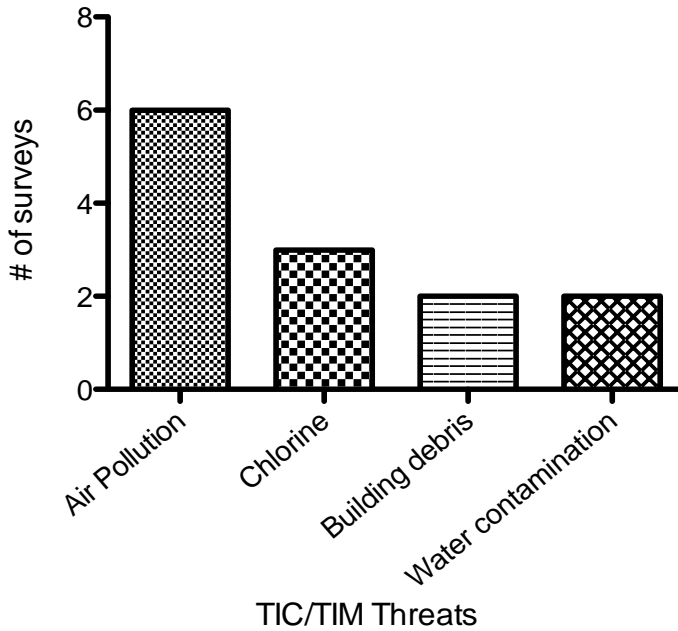
Part II: Session 1: TIC/TIM Threats Related to Megacity OE

1)   In order of priority, what are your top four TIC/TIM threats in Megacity environments?

# of surveys (y-axis: 0 to 8)

Categories: Air Pollution (6), Chlorine (3), Building debris (2), Water contamination (2)

TIC/TIM Threats

2)   What methods exist to prioritize diagnostic/prognostic indicators of adverse health effects after exposure to TICs/TIMs?

There are many sensors available that are EPA and FDA approved that can take a variety of sample types and diagnose adverse health effects. The limitation is the number of assays one sensor can do. Ideally, they would be multiplexed and there is the possibility of industry to re-engineer them to make it possible. There are sensors that measure biomarkers, such as heart rate and skin temperature on the individual soldier. There are also sensors that can monitor environmental threats.

3)   What policies, procedures, and concepts of operations need to be addressed?

There needs to be better biomonitoring of the individual soldier for the purposes of tracking exposure incidents. There also needs be policies put in place that guide biomarker thresholds in conjunction with the biomonitoring. Additionally, there needs to be a development of actionable metrics that are indicators of environmental threats and exposures.

4)   How can existing or future biosurveillance tools address a deployment operation in the Megacity OE?

Future biosurveillance tools should focus on environmental detection, physiological measurements related to biomarkers, and GPS for location purposes. Ideally these tools will be miniaturized and digital and able to collect real-time data.

Part III: Session 2: Using Far forward Diagnostics in Non-Agent Chemical Exposure (TIC/TIM) Scenarios

1)   What are the top, prioritized health effects that need far forward diagnostics in the Megacity OE?

The top health effect that needs far-forward diagnostics would be pulmonary distress. Exposure to chemicals or irritants that lead to lung injury need early detection biomarkers for screening. There was also a concern about kidney degradation.
Additionally, there is a need to conduct environmental surveillance prior to conducting operations to avoid exposure events to toxic chemicals. There are also concerns about lead exposure, sanitation, and water/airborne pathogens.

2)   What existing technologies and diagnostic tools need to be advanced far forward?

Handheld detectors and wearable environmental sensors both need to be advanced for purposes of monitoring the soldier and the environment. The iSTAT and the Alere triage are two examples of hand held monitors that need advancement. Rapid detection is critical for all sensors.

3)   How must existing diagnostic devices be adapted for use in theater?

There are many critical requirements that make a device field ready for use in theatre. Some of these attributes include being lightweight, smaller, and able to provide a quick, simple, and actionable result. These devices need to be more rugged and run on low power requirements, as well as be network compatible.

4)   Should the diagnostic tools be anchored to Adverse Outcome Pathways (AOPs)?
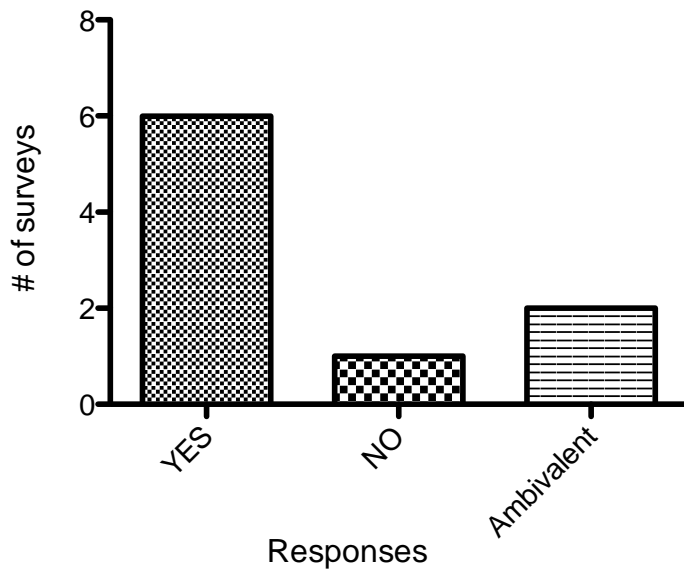
Part IV: Session 3: Personalized medicine solutions for environmental health and protection

1)   What research areas show the most promise in determining susceptibility?

Genetics and Epigenetics are the two main areas that show the most promise in determining susceptibility in an individual.

2)   What diagnostic indicators are most important for identifying potential susceptibility? Are there set standards for certain populations including the military?

Genomic sequencing, screening of actionable variants, and exposure history are the most important diagnostic indicators for identifying susceptibility.

3)   How will personalized medicine and the determination of individual susceptibility impact the military?

There were differences of opinions here. Some believe that personalized medicine should not impede the demands of the military operations and it should only be executed when detection, the implementation processes, and benefits are sufficiently clear. Another person stipulated that this is a new field that will continue to change and it will take approximately 3-7 years to mature before becoming fully utilized. There were several people who recognized the potential of personalized medicine by identifying its utility regarding placement in missions, risk assessments, and lowering the health costs for service members and ultimately the DoD.

4)   When comparing the level of effect with the likelihood of an event, what should be of the highest concern when developing intervention of treatment strategies (e.g. lower likelihood incapacitation vs. higher likelihood performance)?

The general consensus is that priority should be given to high likelihood and high impact events based on the level of effect.

5)   What new considerations should be given in the evolution of a Force Health Protection plan to longitudinally monitor exposures to TICs and TIMs?

A database of likely exposures needs to be established, based on intelligence data and environmental monitoring. One possibility would be to set up longitudinal monitoring by taking biological samples before and after exposures, so there is a baseline against which to compare.

Part V: Conference Overview Questions

1)   Given the Megacity OE, what are the top chronic health effects that you are most concerned with and what is the actionable information that personalized medicine could address/prevent?
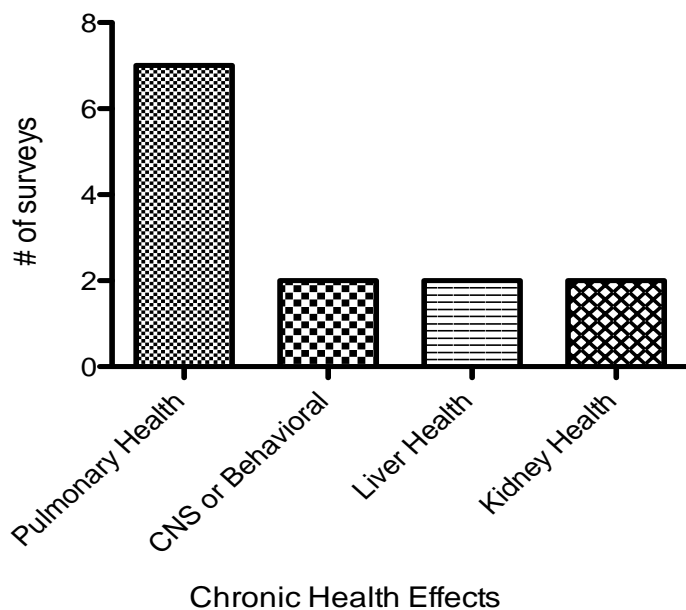
2)   Given the Megacity OE, what are the acute health effects that you are most concerned with and what is the actionable information that biomarkers could address/prevent?

The main concern regarding acute health effects is the exposure to industrial chemicals, including chlorine and toxic dust. Any health effect that makes a unit non-mission capable is a major concern. Exposures from localized sources, including sanitation were also a concern. There is a need to identify biomarkers that occur at key points in AOPs and they apply to many potential exposure hazards.

3)   Given the Megacity OE, what are the top chronic health effects that you are most concerned with and what is the actionable information that biomarkers could address/prevent?

Resoundingly, the most reported concern regarding long-term health effects includes poor air quality and potential chemical exposures. There was also a mention of PTSD as well as prolonged exposure to certain pollutants and long-term outcomes.

6. LESSON LEARNED (HOTWASH)

Overall, the feedback received by attendees was generally positive and the workshop was well received. Things to consider for future events:
- Need more than 25 minutes for topics in the future
- Plan what information is relevant and how would be the best way of presenting that to fill the needs.
    - Adding planning pieces, talking about S&T gaps up front
    - Better define the concept of exposures to set the stage
        - As far as developing a research plan, all three main areas discussed in the workshop are important.
        - Discuss how we can advance initiatives if there's a lack of JPEO or other big program to transition off to.
    - The specifics on finding a "magic biomarker" are not realistic.
    - Think about the medical groups and a medical application of technology for preventive medicine both in military and civilian worlds.
    - Provide scenarios to talk about and identify realistic solutions. Ask the question: What would you like to have? Look at this in full spectrum of mission operations, planning, monitoring, and future symptoms that could arise.
    - Make sure to divide those associated with preventive medicine uniformly amongst the working groups.
    - Better to look at research roadmap in DoD framework, not just medical for health effects.
    - Separate exposure problems that may result in future diseases and exposure problems that are accidental. How do you design something to deal with both situations and integrate them? Environmental monitoring and individual biomonitoring? It appears there is an opportunity to do broader thinking on how to address all of these topics.
        - If we had a consensus on prioritized health effects, it would go a long way in planning. How do we engage community to generate a priority list?
        - Community doesn't necessarily know what they need.
        - How are we going to get at the health effects aspect?
    - What should we be advancing technology wise? If you could take a clinical assay relevant to health and push it far forward, what would it be? Look for earlier markers of injuries.
    - Top five acute and long term health effects? What criteria should be used in evaluating this?
    - Clarify what our mission is. Top 5 health effects in megacity environments?
        - Not air monitoring or drinking water
    - Dr. Kingston should write a statement on how his research could support work. Detection tool capability?
    - Exposome ties into microbiome.
        - So many questions, hard to tie into a road map
        - Exposome will be different for every solider
    - Mass spec will not be far forward anytime soon. Should we be considering methods going forward?

- o Blood spots to allow for shipping? Sample collection?
    - Blood spot is becoming more important, ambient temperature, and fixed space.
  - o Exposure reconstruction? Where does USACEHER fit in? Do we need to consider a bioexposure health record?
  - o The limiting factor is how samples are collected, stored, archived and used as actionable?
    - Start small, think of operating base with decent infrastructure.
  - o Does our survey have a question about what study would you design to increase occupational health awareness? What would it be? Sample collection?
    - Firing range, lead levels
  - o Serum repository, what ways can we leverage that? Can we create our own?
  - o Do we make a political push to get the capital to go after that sample bank or make your own?
  - o Digital medicine, such as wearables, should have been better represented at the meeting.
  - o Individual susceptibility to TICs and TIMs should have been better explored in the personalized medicine section.
- Time for attendees to fill out surveys should have been set aside during the meeting to optimize the number of surveys completed.
- The scenario should have been rehearsed and discussed amongst the presenters prior to execution. This was mostly due to limited time, but it would have made the working group discussions more consistent.

APPENDIX A. ATTENDEE SURVEY

U.S. Army Center for Environmental Health Research (USACEHR)
Johns Hopkins University Applied Physics Laboratory (JHU-APL)

State of the Science Workshop to Discuss Environmental Health and Protection: *Personalized Tools to Support Potential and Actual Health Hazards in the Megacity Operational Environment*

Instructions

Overall Goal: The overarching goal of the workshop is to facilitate scientific discussion of these issues and the scientific challenges they pose for assessing health hazards of chemicals.

Outcome/Deliverable: The anticipated end products of the workshop are a series of peer-reviewed position papers, on the state of the science of the key topics listed above, which will communicate a clear research strategy to key leaders and decision makers.

Part I: Professional Background

1) _____ **What is your current field of expertise?**

   a. Environmental Health

   b. Bio-surveillance

   c. Diagnostics

   d. Other:

2) _____ **How long have you been working in your current field?**

   a. 0-5 years

   b. 6-10 years

   c. 11-20 years

   d. 21+ years

3) _____ **What role do you play in your current field?**

   a. Leadership

   b. Operational

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    c.   Basic Research

    d.   Other:

4)   _____   **What is your current status?**

    a.   Active Duty/ Retired Military

    b.   Academia

    c.   Civilian/ Government Contractor

    d.   Private/Industry

Part II: Session 1: TIC/TIM Threats Related to Megacity Operational Environment

1)   _____   **In order of priority, what are your top four TIC/TIM threats in Megacity environments?**

    a. _____

    b. _____

    c. _____

    d. _____

2)   _____   **What methods exist to prioritize diagnostic/prognostic indicators of adverse health effects after exposure to TIC/TIMs?**

3)   _____   **What policies, procedures, and concepts of operations need to be addressed?**

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4) _____ **How can existing or future biosurveillance tools address a deployment operation in the Megacity OE?**

Part III: Session 2: Using Far-Forward Diagnostics in Non-Agent Chemical Exposure (TIC/TIM) Scenarios

1) _____ **What are the top, prioritized health effects that need far-forward diagnostics in the Megacity OE?**

    a. _____

    b. _____

    c. _____

    d. _____

    e. _____

2) _____ **What existing technologies and diagnostic tools need to be advanced far forward?**

    a. _____

    b. _____

    c. _____

    d. _____

    e. _____

3) _____ **How must existing diagnostic devices be adapted for use in theater?**

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4) _____ Should the diagnostic tools be anchored to Adverse Outcome Pathways (AOPs)?

    a. Yes. Please explain:

    d. No. Please explain:

Part IV: Session 3: Personalized medicine solutions for environmental health and protection

1) _____ What research areas show the most promise in determining susceptibility?

    What diagnostic indicators are most important for identifying potential susceptibility?

2) _____ Are there set standards for certain populations including the military?

    How will personalized medicine and the determination of individual susceptibility impact

3) _____ the military?

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4) _____ When comparing the level of effect with the likelihood of an event, what should be of the highest concern when developing intervention of treatment strategies (e.g. lower likelihood incapacitation vs. higher likelihood performance)?

5) _____ What new considerations should be given in the evolution of a Force Health Protection plan to longitudinally monitor exposures to TICs and TIMs?

Part V: Conference Overview Questions

1)   _____   **Given the Megacity operational environment, what are the top chronic health effects that you are most concerned with and what is the actionable information that personalized medicine could address/prevent?**

2)   _____   **Given the Megacity operational environment, what are the acute health effects that you are most concerned with and what is the actionable information that biomarkers could address/prevent?**

3)   _____   **Given the Megacity operational environment, what are the top chronic health effects that you are most concerned with and what is the actionable information that biomarkers could address/prevent?**