Assessing physiological response to toxic industrial chemical exposure in megacities

**Abstract**

Megacities—urban areas with populations of ten million or greater—and other dense urban environments are emerging and growing globally, posing new challenges for U.S. military operations. The United States (U.S.) military can be better positioned for potential future operations within megacities as part of a joint, interagency, intergovernmental, and multinational team by increasing its understanding of megacity environments (Harris et al., 2014). Chemical exposures pose risk to the health and readiness of Service Members operating in these environments. The Naval Research Laboratory (NRL) prioritized a list of the top 30 chemicals of concern for global military operations based on physical characteristics and available toxicology data (Sutto, 2015). Occupational exposure to these chemicals increases risk of developing adverse health effects during mission operations or post-deployment. Policy guidelines specifying the use of the appropriate personal protective gear constitute the first line of defense to protect personnel by limiting exposure in the field. After a confirmed or suspected exposure event, far-forward diagnostic tools are needed.
Assessing Physiological Response to Toxic Industrial Chemical Exposure in Megacities

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Introduction

Megacities—urban areas with populations of ten million or greater—and other dense urban environments are emerging and growing globally, posing new challenges for U.S. military operations. The United States (U.S.) military can be better positioned for potential future operations within megacities as part of a joint, interagency, intergovernmental, and multinational team by increasing its understanding of megacity environments (Harris et al., 2014). Chemical exposures pose risk to the health and readiness of Service Members operating in these environments. The Naval Research Laboratory (NRL) prioritized a list of the top 30 chemicals of concern for global military operations based on physical characteristics and available toxicology data (Sutto, 2015). Occupational exposure to these chemicals increases risk of developing adverse health effects during mission operations or post-deployment. Policy guidelines specifying the use of the appropriate personal protective gear constitute the first line of defense to protect personnel by limiting exposure in the field. After a confirmed or suspected exposure event, far-forward diagnostic tools are needed to quickly and effectively determine and manage the risk of adverse health effects post-exposure in order to make informed command decisions about return-to-duty and treatment options. Identifying and quantifying biomolecular indicators in accessible biofluids such as blood, saliva, or urine is critically important for evaluating chemically-induced disease prognosis (Tawa et al., 2014; Ippolito et al., 2015). Biomarkers of end-organ toxicity can be integrated into a fieldable detection system to rapidly diagnose chemical exposure-induced adverse health effects in theater. Noninvasive or minimally invasive screening methods could enable early intervention, treatment, and informed decision making to optimize force readiness. Mapping biomolecular patterns of adverse health effects represents a promising solution to the complex problem of assessing health effects after exposure to mixtures of different chemicals and /or pollutants and aggregated exposure effects over time (Silins & Högberg, 2011).

This systematic literature review identifies and assesses the level of evidence for candidate far forward diagnostic technologies and biomarkers that may be used to detect emerging health effects from exposure to militarily-relevant chemicals. The review emphasizes a subacute exposure window (i.e., days to weeks) best suited to the short-term exposure scenarios anticipated in military operations and mission scenarios. Biomarker development demands meeting rigorous regulatory and clinical standards before adoption in the field, but military investment in this research and development process has the potential for significant returns in military healthcare during the deployment life cycle. Biomarker-based screening technologies can benefit routine health care screening, return-to-duty decision-making, triage during mass casualty exposure events, and/or guiding the development of diagnostics to inform treatment options. Biomarker-based far-forward diagnostic strategies and technologies have the potential to transform military healthcare in the changing face of warfare in megacities and dense urban operating environments.

Methods

The peer-reviewed literature was surveyed to evaluate the weight-of-evidence regarding biomarkers for emerging health effects resulting from exposure to militarily-relevant chemicals (Table 1). The target list of militarily relevant chemicals was based on 30 prioritized megacity chemical hazards outlined in the NRL Industrial Chemical Assessment for Hazard, Probability, and Biomarker Prioritization (Sutto, 2015). A biomarker was defined as a molecular, cellular, or biophysical event linked to an emerging health effect.
Databases searched included PubMed, Web of Knowledge, Google Scholar, ClinicalTrials.gov, publicly available Department of Defense (DoD) technical reports (e.g., Defense Technical Information Center), non-DoD sources, and the Center for Disease Control Agency for Toxic Substance & Disease Registry and from the U.S. Library of Medicine Hazardous Substances Data Bank (“Agency for Toxic Substance & Disease Registry - Medical Management Guidelines Home Page,” n.d., “U.S. National Library of Medicine - Hazardous Substances Data Bank,” n.d.). Search terms were selected to identify studies that examined health effects associated with exposure to the high priority chemicals. The search was limited to articles published in English from January 2005 to May 2015.

Peer-reviewed articles were excluded if they (1) reported acute responses requiring immediate palliative care, (2) reviewed in vitro or computational toxicology sites that did not use publically available data sets, and (3) discussed mechanistic biomarkers without clear implications for candidate prognostic markers suitable for fieldable detection devices.

An objective two-step grading approach based on the U.S. Preventive Services Task Force Grade Definitions was used to assess the internal validity of individual studies published in peer-reviewed journal articles that met the inclusion criteria. The first step in evidence grading methodology identified and ranked the study design within a hierarchy of evidence, and the second step assessed the study quality (good, fair, poor). Study designs included the following categories: preclinical research (e.g., animal models), clinical research (e.g., clinical trials, diagnostic studies), epidemiological research (e.g., cohort studies, intervention studies), and secondary research (e.g., meta-analysis, systematic reviews). If a publication contained both a preclinical study and a clinical study, a separate grade was assigned for each study.

**Results and Discussion**

A review of 57 current papers in the diagnostic device literature identified five classes of biomarker detection devices (Figure 1). Most of the devices in development are lab-on-a-chip designs and paper-based lab-on-a-chip (LOC paper) prototypes. Frequently portable and disposable, these designs may be amenable to military field settings (Shafiee et al., 2015). Unique technological challenges limit the utility of many prototype diagnostics for use in a far-forward operational setting. Further research, clinical trials, and validation are needed to advance the devices beyond the prototype stage (Hoenigl et al., 2014). Ruggedization and miniaturization of laboratory prototypes are significant challenges in fielding these devices (Greenwood et al., 2007).
Table 2 lists the target organs of adverse health effects following exposure to each of the chemicals. Table 3 reports the key acute, subacute, and chronic health effects for each target organ. Most of the data summarized in Tables 2 and 3 are derived from a scan of public toxicology data repositories (e.g., the Hazardous Substances Data Bank and related ToxNet resources). These repositories identify relevant studies outside the time frame of the systematic review (i.e., before 2005-2015).
Articles meeting the inclusion criteria for adverse health effects were organized into eight specific target organ categories: lung, central nervous system (CNS), peripheral nervous system (PNS), heart, liver, kidney, gastrointestinal, other, and multiple (Figure 2). A summary of the literature review by target organ for five key target organs (lung, CNS/PNS, heart, liver, and kidney) follows.

**Lung.** Several of the 28 lung-related articles identified biomarkers correlating with acute lung injury/acute respiratory distress syndrome (ALI/ARDS): RAGE, ICAM-1, KL-6, SP-D, vWF, IL-6, IL-8, protein C, PAI-1, TNFR1 and 2, and thrombomodulin (Agrawal et al., 2012; Calfee et al., 2008; Calfee et al., 2009; Collard et al., 2010; McClintock et al., 2008; Parsons et al., 2005; Uchida et al., 2006). Many of these biomarkers were associated with clinical outcomes (e.g., ventilator-free days, organ-failure-free days, and mortality). Mean levels the proteins PBEF or MIF were significantly greater in serum of ALI patients than healthy controls although the specificity for ALI remains uncertain (Gao et al., 2007; Ye et al., 2005). Combining predictive markers improved predictive power. Low levels of protein C and high levels of PAI-1 were independent predictors of mortality, and the two markers had a synergistic interaction for the risk of death (Ware et al., 2007). Levels of RAGE, PCP III, BNP, ANG-2, IL-8, TNF-α, and IL-10 show potential as a diagnostic biomarker panel (Fremont et al., 2010). In two studies, combinations of clinical predictors and multiple plasma biomarkers measured in individuals with ALI/ARDS improved predictive power for mortality over either approach alone, with some evidence that trauma differentially affects odds of mortality (Calfee et al., 2011; Ware et al., 2010). Exposure to isocyanates (e.g., TDI and MDI) was linked to occupational asthma. Biomarkers associated with this clinical
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megacity operational environments with increased risk of non-agent chemical exposure. Further research is needed to ensure the

throughout the soldier deployment life cycle to inform medical decisions during and after exposure events, especially in polluted

protein after TCE exposure (Vermeulen et al., 2012). Urinary panels include Alb, NAG and

Clinical studies have identified promising urinary biomarkers of acute kidney injury and/or nephrotoxicity, including KIM-1

Kidney. The 17 kidney-related articles identified biomarkers in serum and urine. Acute kidney injury markers in serum included

Liver. Four articles identified liver biomarkers in serum, including miRNAs (serum miR-125a-5p, miR-192 and miRNA-122; Zheng et al., 2015; Zhang et al., 2010). Changes in miRNA levels assessed in liver tissue implicate miRNAs such as miR-34a as promising new candidates in serum or urine (Koufaris et al., 2012). Liver injury diagnosis is routinely made in conjunction with clinical chemistry data, including alanine amino transferase (ALT). A panel of plasma or serum biomarkers diagnosed liver fibrosis in animal models (fibrinogen precursor, ceruloplasmin isoform 1, insulin like growth factor binding protein, alpha-2-macroglobulin, and vitronectin) (Ippolito et al., 2015).

Kidney. The 17 kidney-related articles identified biomarkers in serum and urine. Acute kidney injury markers in serum included LG3, cathepsin L, NGAL, IL-6, soluble TNFR1 and 2, and PAI-1 as potential candidates (Haase et al, 2014; Liu et al., 2007). Clinical studies have identified promising urinary biomarkers of acute kidney injury and/or nephrotoxicity, including KIM-1 protein after TCE exposure (Vermeulen et al., 2012). Urinary panels include Alb, NAG and α1-MG as indicators of fluoride and arsenic-induced glomerular and tubular injury (Zeng et al., 2014). KIM-1 predicted kidney injury earlier than the traditional biomarkers, such as creatinine, BUN, and/or NGAL (Rached et al., 2008; Vaidya et al., 2010; Wunnapuk, Gobe, et al., 2014; Zhou et al., 2008). Many of the preclinical studies examined urinary biomarkers of kidney injury other than KIM-1 (e.g., Cal, Clu, KIM-1, Lcn2, the three-branched chain amino acids [leucine, isoleucine, and valine], OPN, TTF3) and provide important foundational information (Boudonck et al., 2009; Fuchs et al., 2014; Hoffmann et al., 2010; Wunnapuk, Liu, et al., 2014; Yu et al., 2010).

Other health effects. Other health effects with biomarker candidates included gastrointestinal, reproductive, cancer progression,

Other health effects with biomarker candidates included gastrointestinal, reproductive, cancer progression, blood, bone, and lymphatics (see Tables 2 and 3 and Figure 2).

Conclusions

As megacities and dense urban environments continue to grow in number and population size, there is an unmet need to understand the health threats of service members exposed to toxic chemicals and environmental hazards unique to the megacity operational environment. Properly validated biomarkers of exposure and effect can integrate with current biomonitoring systems throughout the soldier deployment life cycle to inform medical decisions during and after exposure events, especially in polluted megacity operational environments with increased risk of non-agent chemical exposure. Further research is needed to ensure the fieldability of ruggedized detection systems in the megacity environment.
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The views, opinions, and/or findings contained in this report are those of the author and should not be construed as official Department of the Army position, policy, or decision, unless so designated by other official documentation.

Acronyms and Abbreviations

AChE  Acetylcholinesterase
Alb   Albumin
ALI   Acute Lung Injury
ALP   Alkaline Phosphatase
ALT   Alanine Aminotransferase
ANG-2 Angiopoietin-2
ARDS  Acute Respiratory Distress Syndrome
AST   Aspartate Aminotransferase
BNP   B-type Natriuretic Protein
BUN   Blood Urea Concentration
Cal   Calbindin-D28
CC16  Clara Cell 16
ChAT  Choline Acetyltransferase
ChE   Cholinesterase
CI    Confidence Interval
CK    Cytokeratin
Clu   Clusterin
CNS   Central Nervous System
CO    Carbon Monoxide
COR1A Coronin 1A
COX2  Cyclooxygenase Type 2
CPK   Creatine Kinase
DNA   Deoxyribonucleic acid
ECG   Electrocardiogram
eCO₂  Exhaled Carbon Dioxide
eNO   Exhaled Nitric Oxide
F₂-IsoP F₂-Isoprostanes
GFAP  Glial Fibrillary Acidic Protein
GRIA 1 Glutamate Receptor 1
HPX   Hemopexin
HSA     Human Serum Albumin
ICAM-1 Intercellular Adhesion Molecule-1
IL       Interleukin
KIM-1    Kidney Injury Molecule-1
Lcn2     Lipocalin 2
LG3      Prelecan C-terminal Fragment LG3
LPO      Lipid Peroxidation
LSP-1    Lymphocyte Specific Protein-1
LysoPC   Lysophosphatidylcholine
MBP      Myelin Basic Protein
MDI      Methylene Diphenyl Diisocyanate
MIF      Migration Inhibitory Factor
miRNA    micro-Ribonucleic Acid
MMP-9    Matrix Metalloproteinase-9
MPO      Myeloperoxidase
NAG      N-Acetyl-β-D-Glucosaminidase
NFP      Neurofilament Triplet Proteins
NGAL     Neutrophil Gelatinase-associated Lipocalin
NMP22    Nuclear Matrix Protein-22
NO₂      Nitrogen Dioxide
OP       Organophosphate
PAI-1    Plasminogen Activator Inhibitor-1
PBEF     Pre-B-Cell Colony-Enhancing Factor
PCP III  Procollagen Peptide III
PNS      Peripheral Nervous System
RAGE     Receptor for Advanced Glycation Endproducts
S100B    S100 Calcium-Binding Protein B
SOD      Superoxide Dismutase
SP       Surfactant Protein
TCE      Trichloroethylene
TDI      Toluene-2,4-Diisocyanate
TFF3     Trefoil Factor 3
TIC      Toxic industrial chemical
TIM      Toxic industrial material
TNFR     Tumor Necrosis Factor Receptor
TNI  Troponin I
Tp-e  T_peak - T_end
U.S. United States
USACEHR United States Army Center for Environmental Health Research
VDBP  Vitamin-D-Binding Protein
VEGF  Vascular Endothelial Growth Factor
vWF  von Willebrand Factor
α1-MG  α-1-microglobulin

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