Current DoD Research and Evaluation Using Non-animal Methods in Support of Hazard Assessment

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The author review and summary of the Congressionally Directed Medical Research Programs (CDMRP) and the Toxic Exposures Research Program (TERP) do not necessarily reflect the opinions and views of the CDMRP and TERP.

Military Environments = Unique Situations

Chemical Stressors

Photo credit: Tristin English

- Fuels
- Exhausts/combustion products
- Pesticides
- Particulate Matter
- Metals
- Paints, coatings
- Industrial chemicals

Physical Stressors

U.S. Navy photo by Mass Communication Specialist 3rd Chris Cavagnaro/Released

- Altitude
- Extreme temperatures
- Noise
- Vibration
- Fatigue

Combinations/ Co-stressors

U.S. Navy photo by Mass Communication Specialist 3rd Class Roland John/Released

Outline

- DoD Biomedical Research/Evaluation Enterprise
- Performance related outcomes
  - Exposure monitoring
  - Chronic effects from short term exposures
- Currently fielded non-animal methods
- Approaches under development
- Summary

DoD Biomedical/Operational/Environmental Sciences Enterprise

- U.S. Army
  - Army Research Laboratory
  - ★ U.S. Army Combat Capabilities Development Command (DEVCOM)
    - ✓ Soldier Center
      - – Warfighter Protection
    - ✓ Chemical Biological Center (CBC)
      - – Sensors/detection

- U.S. Navy
  - Navy Research Laboratory
    - ✓ Monitoring/Sensors
      - – Contaminants
  - ★ Naval Medical Research Unit-Dayton
    - ✓ NAMRU-Dayton

- U.S. Air Force
  - Air Force Research Laboratory
    - ★ ✓ 711th Human Performance Wing

- ★ Defense Health Agency
  - Uniformed Services University of the Health Sciences
  - Medical Research and Development
    - ✓ Research Institute for Chemical Defense
    - ✓ Walter Reed Institute for Research
  - Defense Centers for Public Health
    - ✓ Aberdeen
    - ✓ Dayton

- ★ Veteran Affairs

★ DoD TriServices Toxicology Consortium

Congressionally Directed Medical Research Programs (CDMRP)

38 Funded Research Programs

Alcohol and Substance Use Disorders
Amyotrophic Lateral Sclerosis
Autism
Bone Marrow Failure
Breast Cancer
Chronic Pain Management
Combat Readiness-Medical
Duchenne Muscular Dystrophy
Epilepsy
Gulf War Illness
Hearing Restoration
Joint Warfighter Medical
Kidney Cancer
Lung Cancer
Lupus
Melanoma
Military Burn
Multiple Sclerosis
Neurofibromatosis

Neurotoxin Exposure Treatment Parkinson
Orthotics and Prosthetics Outcomes
Ovarian Cancer
Pancreatic Cancer
Parkinson
Peer Reviewed Alzheimer
Peer Reviewed Cancer
Peer Reviewed Medical
Peer Reviewed Orthopedic
Prostate Cancer
Rare Cancers
Reconstructive Transplant Research
Scleroderma
Spinal Cord Injury
Tick-Borne Disease
Toxic Exposures
Traumatic Brain Injury and Psychological Health
Tuberous Sclerosis Complex
Vision

Toxic Exposures Research Program (TERP)

- $30M appropriation
- Support for:
  - Gulf War Illness
  - Burn pits and other airborne hazards
  - Neurotoxin exposures
- Other toxic exposures in general, including prophylactic medications, pesticides, organophosphates, toxic industrial chemicals, materials, metals, and minerals
- Focus on speeding development of treatments, cures, and preventions = maximum benefit to Service members, Veterans, and the American public

CDMRP-Military Operational Medicine Research Program

End State Goal: Optimize health readiness and performance across environmental extremes to maximize warfighter and unit lethality.

Functional Objective: Prevent illness and optimize performance when operating in environmentally toxic environments.

TO ID	Environmental Toxic Exposures Research Technical Objective (TO)
1.4.1	Identify and develop assays for verified biomarkers of exposures to military-relevant chemicals, materials, or mixtures. TRL 1-3
1.4.2	Identify/improve and demonstrate technology for rapid screening of toxic chemicals and materials. TRL 3-5
1.4.3	Provide novel health or toxicological data to fill data gaps for militarily-relevant chemicals, materials, and environmental hazards to advise on exposure limits and guidelines. TRL 3-5

Comparative Analysis of PFAS (and Other Toxic Chemicals) in Blood

- Service Member and Veterans preventive healthcare is strengthened when a diagnosed medical condition is associated with a prior exposure.
- Investigate Dried Blood Spot (DBS) sampling for monitoring a variety of military toxicants.
- In a VA collaboration, DBS proof-of-concept analyses of plasma and DBS will seek to quantify analytes associated with exposure and adverse effect biomarkers.
- Building on DoD PFAS screening practices, a VA and DCPH-A TOX collaboration will:
  - Expand the number of PFAS chemicals measured in blood and DBS.
  - Identify other increased non-PFAS in firefighter blood and DBS specimens.
  - Correlate measurements between plasma and DBS.
  - Strengthen toxicological understanding and relevance of select PFAS levels and an increased risk of adverse health outcomes.
  - Investigate biomarkers of toxicity associated with exposure.

- POC: dha.apg.Pub-Health-A.mbx.tox-info@health.mil

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Developmental Environmental Safety and Health Evaluation (DESHE)

- Computational Toxicology
- Mutagenicity (Ames)
  - Nitramine enhanced
- MarBL (Marine Bio-Luminescence Assay)
- Skin Sensitization
- Skin Irritation
- Phototoxicity
- CAOTE (cell-based approximate oral toxicity estimate)
- Dermal Toxicity

HHA/TC - Health Hazard Assessment;
NEPA - National Environmental Policy Act;
LCEA – Life Cycle Environmental Assessment;
BA – Budget Activity

Phases and testing

LLM-105
Wang et al. 2018

BA1
- Computational **predictions** from chemical/physical performance parameters and toxicity

BA2
- **Experimental values** of chemical and physical characteristics
- *In vitro* **toxicity screening** methods
- **Acute toxicity data** (optional)
- *Computational predictions from chemical/physical performance parameters and toxicity*
- **Professional judgment**

BA3
- In vivo **toxicity testing; acute, sub-acute**
- **Biodegradation** in various media
- **Ecotoxicity**
- *Computational predictions from chemical/physical performance parameters and toxicity*
- *Experimental values of chemical and physical characteristics*
- *In-vitro toxicity screening methods*
- Professional judgment

BA4
- **Sub-chronic, chronic toxicity**
- **Occupational exposure studies**, including absorption tests
- Ecotoxicity in multiple species
- *Computational predictions from chemical/physical performance parameters and toxicity*
- *Experimental values of chemical and physical characteristics*
- *In-vitro toxicity screening methods*
- *In vivo toxicity testing; acute, sub-acute toxicity data*
- *Biodegradation in various media, persistence*
- *Professional judgment*

BA5+
Acquisition Documentation Requirements (AR 70-1, MIL-STD-882E, DODI 5000.02)
- **PESHE**
- **HHA/TC**
- **NEPA**
- **LCEA**
- Environmental permits

Milestone A — (TRL 1) — (TRL 2-3) — (TRL 4,5,6) — (TRL 6,7) — Milestone B — (TRL 8)

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Military Personnel = Unique Expectations

- What measures or endpoints best represent Service Member (or First Responder) effects, needs and concerns?
  - Are we including the right combinations?
  - Do conventional measures capture relevant impacts?
    - ✓ Physical performance effects
    - ✓ Cognitive performance effects
    - ✓ Circadian toxicity
- Do conventional measures capture readiness?
- Would our measures capture "subtle" effects before failure?
- Do our measures capture the correct timing of effects?
  - Acute, Chronic, Immediate, During Operations/Missions, Delayed

Mode/Mechanism of Action

- Vanadium Oxide (V_2O_5)
  - Modes of Action (MOA) - PO_4^{-3} and selenium mimic, inhibits phosphatases and MAP kinases.
- Is it a Class 2B carcinogen? Evidence is mixed – use alternative methods to better characterize the potential for inflammation-based cancer MOA.
  - Toxicity prediction using QSAR and GenRA, in vitro testing (EpiAirway FT) viability, TEER, cytokine production (NAMRU-Dayton)
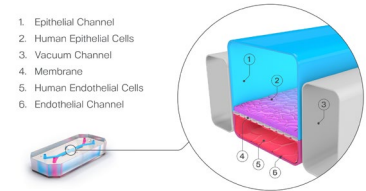
In Silico Approaches

- 711th Wing Air Force
  - QSAR Toolkit

- Protein/ligand binding to screen
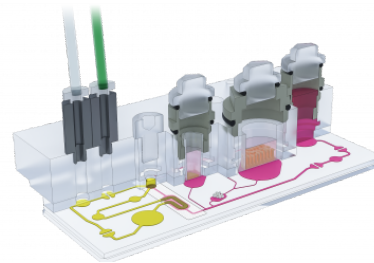 - Neurotoxicity
  - Receptor toxicology

Microphysiological Systems

- Cardiac
- Liver
- Lung
- Dermal
- Kidney
- Intestinal
- CNS
- BBB
- Aerosol exposure

- POC - DEVCOM-CBC

Emulate

1. Epithelial Channel
2. Human Epithelial Cells
3. Vacuum Channel
4. Membrane
5. Human Endothelial Cells
6. Endothelial Channel

TissUse

CN Bio

PhysioMimix™ OOC
A CN BIO INNOVATION

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Summary

- Substantial and enduring efforts to:
  - Characterize hazards to the Warfighter, workforce and associated communities
  - Invest in new technologies and approaches
    - ✓ Biorepository sampling
    - ✓ Wearables/sensors to capture exposure
    - ✓ In vitro and microphysiological systems as systemic toxicity surrogates
    - ✓ Computational approaches to predict future hazards

Improving Health and Building Readiness. Anytime, Anywhere — Always

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- Sources for this presentation include:
  - https://myarmybenefits.us.army.mil/News/Exposure-Record-Supports-Veterans-Health-by-Tracking-Exposure-Events
  - https://www.army.mil/devcom
  - https://cdmrp.health.mil/
  - https://cdmrp.health.mil/MBRP/pbks/FY22%20MBRP%20Stakeholders%20MFR.pdf