Military Toxicology – Army Public Health Center/
Tri-Service Toxicology Consortium

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Director, Toxicology
Army Public Health Center

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Strategic Goal: Encourage the adoption and use of new methods and approaches by federal agencies and regulated industries.

- Agencies should adopt clear language regarding the acceptance of NAMs.

- Agencies should collaborate with international partners to facilitate global harmonization and regulatory acceptance.

- Agencies and stakeholders should work together to explore processes to incentivize and promote the use of NAMs.

- All stakeholders should endeavor to identify appropriate metrics for prioritizing activities, monitoring progress, and measuring success.
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“One Health”

Army scientists collaborate to investigate toxicology

LISA L. MORRIS
ARMY MEDICINE

PERCHLORATE IS A COMMONLY USED OXIDIZER NEEDED FOR SOLID ROCKET ENGINES AND SOME PROFESSIONAL. As extensive as its use is, an increasing number of studies show perchlorate contamination can have negative effects on the environment and human health. It inhibits the function of the thyroid when individuals are consistently exposed at parts per billion levels through the drinking water.

The U.S. Army Public Health Command, Toxicology Portfolio has been working with developers at the Document Research and Development Center to find a replacement for perchlorate that is less toxic and less mobile in the environment. One proposed replacement is pentaborate, explained Dr. Mark Johnson, Toxicology Portfolio director.

"Pentaborate has been evaluated by the Toxicology Portfolio in studies to address human health concerns and makes a recommendation in the form of a Toxicity Assessment. However, inhibitory effects to the thyroid are best evaluated using a sensitive model species," Johnson said.

Bill Brand, Chief, Environmental and Regulatory Affairs Division, oversaw this study.

The IMAPHRP’s role in the study itself includes an extensive preparation period and three 21-day test periods, all of which will take approximately one year to complete.

"We’re really looking forward to this because within the IMAPHRP, we’ve only had this capability," said Col. Thomas Tommas, USAMRIID commander. "We have a very unique aquaculture mission. The IMAPHRP’s unique aquaculture facilities allow their scientists to house and study frogs as opposed to other USAMRIID labs that must study rodents or other small mammals.

With other USAMRIID labs, compared to the IMAPHRP’s unique capabilities, the IMAPHRP will house other veteran scientists to visit and learn from the study.

Bill Brand, USAPHC, contributed to this story.
Range Cleanup Estimates

- Navy - 1.3
  - High cost estimate: $2.50
  - Low cost estimate: $0.20
  - $0.20

- Marine Corps - 1.9
  - High cost estimate: $7
  - Low cost estimate: $0.50
  - $0.50

- Air Force - 6.4
  - High cost estimate: $14
  - Low cost estimate: $1.20
  - $1.20

- Army - 15
  - High cost estimate: $141.50
  - Low cost estimate: $15
  - $15

Billions of dollars

GAO 2004. Operational Ranges Report, 04-0601
New substances

- MDNTO
- DNAM
- 5-AT
- 1-Methyl-5-nitriminotetrazole
- TTA
- DBX-1
- DAAF
- EGDN

Chemical Structures
Army Regulation 40–5
Medical Services

• Preventive Medicine
• Chapter 1: Introduction
• Section I: General
  – 1–5. Preventive medicine policies
    • The army will-
      • m. Ensure that all new chemicals and materials being added to the Army Supply System have a toxicity clearance.
  – 1–7. Preventive medicine programs and services
    • g. Preventive medicine toxicology and laboratory services.
      – (a) Toxicological assessments of potentially hazardous materials.
      – (b) Toxicity clearances for Army chemicals and materiel.
      – (c) Toxicologically based assessments of health risks.
Early integration is the least expensive and most effective way to minimize the downstream cost, schedule, and performance impacts of any weapon system.
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Army Public Health Center

BA1: Basic Research (TRL 1)

BA2: Applied Research (TRL 4, 5, 6)

BA3: Advanced Technology Development & Prototypes (TRL 6, 7)

BA4: Advanced Component Development & Prototypes (TRL 8)

BA5: System Development & Demonstration (TRL 9)

BA7: Operational System Development (TRL 9)

Is ESOH risk acceptable?

Ideal paradigm
Levels of Weapon System/Platform Development

• **Conception** – computer simulation only
• **Synthesis** – labtop operation, small quantities
• **Demonstration/Validation** – refinement of synthesis, stabilization of mixtures, use of COTS.
• **Testing** – System evaluation
• **Production and Use**
• **Demilitarization**
# New Compound Development Process

<table>
<thead>
<tr>
<th>Stage</th>
<th>Action</th>
<th>Data requirement</th>
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<tr>
<td><strong>Conception</strong></td>
<td>In silico approaches (QSAR), read across</td>
<td>Chem/phys. properties</td>
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<td>Human toxicity estimates</td>
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<tr>
<td><strong>Synthesis</strong></td>
<td>Develop empirical</td>
<td>Chem/phys. properties</td>
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<td></td>
<td>Chemical/phys data/</td>
<td>(estimate fate, transport, bioaccumulation)</td>
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<td></td>
<td>in vitro tox (HTS)</td>
<td>Toxicity data, acute</td>
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<td>In vitro screen</td>
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<td><strong>Testing</strong></td>
<td>Tier 1 toxicity testing</td>
<td>Toxicity data, subchronic</td>
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<tr>
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<td>Toxicity data, cancer</td>
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<tr>
<td><strong>Dem/Val</strong></td>
<td>Tier 2 toxicity testing;</td>
<td>Media samples</td>
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<tr>
<td></td>
<td>Tier 1 Ecotox testing</td>
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<tr>
<td><strong>Production</strong></td>
<td>Tier 2 Ecotox testing</td>
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<td></td>
<td>Tier 3 chronic testing</td>
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<tr>
<td><strong>Storage &amp; Use</strong></td>
<td>Monitoring</td>
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<td><strong>Demil</strong></td>
<td>Monitoring</td>
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Application of the Phased Approach to Compound Development

• ASTM E-2552-16 Assessing Environmental and Human Health Impacts of New Compounds for Military Use
  – Toxicology Assessments – technical foundation of ESOH information.

• TTCP (The Technical Cooperative Program), Key Technical Area (KTA) 4-42: Development of a Framework to Assess the Environmental Impacts of Green Munition Constituents and of New energetic Formulations

• NATO/STO AVT – RLS-276 Environmental Management of Munition and Greener Approaches to Design (APG, MD; Bucharest, RU; Rijswijk, NE)
Current efforts

- M115, 116, 177 Simulators
  - Reformulated
- M-18 Smoke Grenade
  - Sulfur – sugar –based fuel
  - New dyes
- Lead-free primers
- IM toxicity data collection
- RDX replacements
Tri-Service Toxicology Consortium

• Army
  – Public Health Center*‡
  – Medical Research Institute of Chemical Defense*‡
  – Edgewood Chemical Biological Center†
  – Center for Environmental Health Research*†
  – Engineering Research and Development Center†

• Navy
  – Navy Medical Research Unit Dayton (NAMRU/Dayton/SA)*†‡
  – Navy and Marine Public Health Center*
  – Naval Surface Warfare Center – Dahlgren†

• Air Force
  – 711 Human Performance Wing
    • School of Aerospace Medicine – Occ Health*/Research Dept.*
    • AFRL – Aerospace Toxicology Program†‡
  – Air Force Civil Engineer Center

† = RDT&E mission
* = Medical COC
Red text – tox laboratory
‡Toxicology service center
• **Mission**: To communicate, coordinate, and optimize toxicology services across the DoD.

• Three meetings/yr.
  – Aberdeen Proving Ground
  – Wright-Patterson AFB
  – SOT (2-hr meeting)

• Format:
  – Day 1: Seminars
  – Day 2: Collaborations/business

• Business
  – “Purpleize” technical reports, exposure benchmarks/peer review
    • Provisional Blood Lead Guidelines for Occupational Monitoring of Lead Exposure in the DoD
    • Evaluation of pharmacokinetic models for the disposition of lead (Pb) in humans, in support of application to occupational exposure limit derivation
• Organ on a chip – ACEHR, AFRL, DARPA, DTRA
• AOPs/Genomics/Proteomics/Metabolomics – ERDC, AFRL, MRICD
• PBPK – NAMRU, AFRL, APHC
• 3-D cultures/slices – AFRL, APHC, CEHR
• *In vitro* cultures – TSTC
• *In silico* (computational toxicology) – AFSAM, AFRL, APHC, ERDC
• Focused *in vivo* – NAMRU, APHC, AFRL, ERDC

*Ecotox receptors*
**Mission**: Promote health and prevent disease, injury, and disability of Soldiers and civilians by specializing and characterizing the toxicity of military-unique compounds and the risks they pose to humans and the environment.

**Toxicology Testing of New Military Materials**
- Computer Modeling
- *In Vivo* Animal Studies
- *In Vitro* Assays
- Toxicity Assessments – RDT&E
- Toxicity Clearances - Acquisition
- Establish safe levels of exposure (Soldiers, Workers, Environment)
Capabilities

- Research Development Testing & Evaluation
- Computer Modeling
- *In Vitro* Assays
- *In Vivo* Studies
- AAALAC & GLP Compliant Laboratories
- QSAR/PBPK/BMDS
TOX Major Projects / Areas of Emphasis for FY18

- **Conserve Warfighters and civilian forces** via studies on toxicology of energetics (e.g., propellants, explosives, pyrotechnics) and fire extinguishers.
  - Continue testing new insensitive munition formulations (IMX-101), fire extinguishing agents, new proposed energetics.
  - Harmonize toxicity data requirements across acquisition and other services.

- **Ensure state-of-science program & facility to meet future needs**
  - Improve and advance methodologies, modeling, and technological capabilities.
  - Enhance internal technical support (pathology/histology, laboratory, veterinary); coordinate toxicology in DoD through TSTC.

- **Improve Toxicology Characterization for New Materials**
  - Deploy state-of-the-science tools to better characterize potential for adverse effects from exposures (soldiers, workers, and their families).
  - Integrate chemical property information in predicting exposures and sustainability.

Support RDT&E and acquisition; Implemented money saving phased approach in ESOH data requirement (what data are needed when)

Conducted over 39 Toxicity Clearances/Assessments for new chemicals for weapon systems/platforms

Published 27 manuscripts/reports:
(15 presentations, platforms, posters)

Conducted 5 in vivo, 10 in vitro studies

DOD-level leadership, coordination & collaboration

Agency/DoD POC for: National Academy of Sciences-Committee on Toxicology, Tri-Service Toxicology Consortium (agency lead); Tri-Service Environmental Risk Assessment Working Group; - Joint Army, Navy, NASA, Air Force (JANNAF) Safety & Environmental Protection Subcommittee

Implement cost-benefit toxicity testing in RDT&E transition to acquisition systems to ensure the health of Warfighters

Prevent release of toxicant by providing timely toxicant information

Preventing entry of toxic systems/platforms into Army supply chain

“Provisional Blood Lead Standards for Occupational Monitoring of Lead Exposure in the DoD”.

*In Vitro* Toxicity Study of New Munition Compounds (BA100-ADN, BA100-BTTN, and BZ1200-CL-20)

Acute Inhalation Toxicity Study in Rats Exposed to Aqueous Agents (Firebane 1179) Used for Automatic Fire Extinguishing Systems

Oral Toxicity of 3-Nitro-1,2,4-triazol-5-one (NTO) in Rats (accepted) Int. J. Toxicology
MRICD Mission and Vision

**Mission**
Discover and develop medical products and knowledge solutions against chemical and biochemical threats via research, education & training, and consultation

**Vision**
To strengthen our Nation and the world by rendering chemical and biochemical threats medically harmless.
Critical studies on RSDL

Pyridostigmine

TestMate® Cholinesterase Kit

Nerve Agent Antidote Kit

Multichambered Autoinjector

Chemical Casualty Care Reference Material

SERPACWA

Convulsant Antidote Nerve Agent (CANA)

Applied Research to Develop Animal Models of Toxicant Exposure

In Advanced Development:
- Advanced Anticonvulsant (AAS, midazolam)
- Bioscavenger (BSCAV, plasma derived hBChE)
- Improved Oxime (INATS, MMB4)
- Centrally Active Therapeutic (INATS, Scopolamine)
US ARMY Center for Environmental Health Research (USACEHR)

Located at Fort Detrick, MD, Subordinate command of the USAMRICD

Mission:

Develop surveillance capabilities to detect, assess, and prevent health effects from adverse environmental, physiological, and psychological exposures.

Three Primary Research Programs:

*Integrative Systems Biology*
  Use of Systems Biology to understand, diagnose, treat military-relevant diseases (e.g. PTSD, traumatic coagulopathy)

*Environmental Health Program*
  Identify molecular response(s) following exposure to environmental hazards (TIC/TIMs, ENM, etc.) in host organisms to inform the development of fieldable diagnostic capabilities, surveillance tools, and adverse health outcome predictions through the utilization of animal models, predictive toxicology methodology, microbiome analysis and end-organ toxicity investigation.

*Pulmonary Health Research Program*
  Biomarkers of occupational and environmental exposures and deployment-related respiratory disease

Hosts Army and USAMRMC Assets:

*Hosts the Army Chief Scientist for Systems Biology*
*Hosts USAMRMC Systems Biology Collaboration Center*
Milestone C approval and expected FY17 fielding of biologically based water toxicity sensor-Environmental Sentinel Biomonitor (ESB).

Developed a panel of molecular biomarkers for clinical assessment of liver fibrosis.

Establishment of gnotobiotic facility for the study of interactions between toxicant exposure and the gut microbiome in humanized mice.

Ongoing development of the zebrafish larva as a high-throughput predictive toxicology tool.

Initiated development of a mobile application providing simplified access to NIOSH Pocket Guide to Chemical Hazards and other relevant chemical databases and exposure standards and guidelines.

Evaluated the toxicity of air-borne dusts from Iraq.

Evaluated the prevalence of asthma, COPD, sarcoid, and other lung diseases in deployed and non-deployed service members to Southwest Asia.
US Army Engineer Research and Development Center

Research Areas
• Civil Works/Water Resources
• Environmental Quality/Installations
• Military Engineering
• Geospatial Research and Engineering

7 Laboratories
2500 Employees

Laboratories
Field Offices
Military Materials in the Environment

Motivation

- Exposure to military materials (i.e., explosives, propellants and smokes) can have detrimental effects on the environment
  - Sustainable use of resources
  - Advancement of environmental assessment, sensing, and decision making
  - Understanding risk of and evolving mitigation and management of existing and emerging chemicals and materials
  - Predictive chemical and toxicological tools for fate, transport and effects

Technical capabilities

- Testing to determine impact of chemicals on aquatic species
- Tools that guide and influence advanced material design
- Technologies to control emerging material transport and demonstrate novel detection, remediation, and mitigation capabilities
- Real-time detection and discrimination methodologies for explosives and mature active range ordnance impact assessment and positioning system
- Tools and guidance to anticipate and adapt to climate change

Payoff

- Sustain training facilities and installations
- Provide cost savings through proactive environmental management of new military materials
- Reduce environmental liability and regulatory constraint
- Improve the speed and safety for fielding new material
- Proactive material and chemical design through early testing of hazard effects
Identified and sequenced genes of novel bacteria KTR9 to degrade RDX in soils

Developed a dual sensor handheld detector for UXO in rough terrain

Developed novel small arms range catch-box material to control lead run-off. Provided scientific assessment of tungsten/nylon bullet preventing costly acquisition action

Electrochemical reduction of RDX in wastewater at Holston AAP; Allowing continued production

Lime technology for reduction of explosives, Redstone Arsenal

Provided low cost procedures for managing catch-box material for DU ranges; APG DU catch-box meets NRC compliance, testing allowed
- Nation's principal research and development resource for non-medical chem-bio (CB) defense.
  - Toxicology of NTEs
  - CBRN
  - Environmental toxicology
    - Decontamination agents
    - Explosives in soils
    - Aquatic toxicology
Mission of the Environmental Health Effects Research Directorate of NAMRU Dayton

To conduct basic and applied toxicology research to assess the risk, or reduce uncertainty in the risk, posed to Department of Defense (DoD) personnel (military and civilian), as well as civilian populations, that are potentially exposed to chemical contaminants and certain physical agents associated with DoD systems and operations.

NAMRU Dayton Mission Statement

To maximize warfighter performance and survivability through premier aeromedical and environmental health research by delivering solutions to the field, the Fleet and for the future.
Recent Contributions/Efforts

- Toxicity evaluation and biomarker identification in rats exposed to burn pit emissions and respirable SW Asian particulate matter. JPC5 Sponsored (Tri-Service Project). FY14-15.
- Relationship between inhalation toxicity and non-constant concentration-time profiles. Sponsored by DTRA via ECBC. Collaborative Project with Army. FY13-15.
- Inhalation toxicity studies in rats and mice for PolyAlphaOlefinic (PAO) fluid. Sponsored by USAF 711th HPW/RHDJ, Collaborative Project, FY15-16.
- Cytotoxicity of nano-sized dental materials and air quality in Area Dental Laboratories. Sponsored by BUMED in collaboration with NAMRU-San Antonio, FY15.
- PBPK model development for metals (consulting role). Sponsored by USACEHR, FY16.
- Role of matrix metalloproteinase-3 in deployment-related pulmonary fibrosis. Sponsored by CDMRP, Collaborative Project with National Jewish Health. FY17-19.
- In vitro toxicity of nanoparticles for photodynamic therapy against combat-associated bacterial and fungal pathogens. Sponsored by MIDRP via NMRČ, Collaborative Project, FY16.
MISSION STATEMENT

Conduct medical, craniofacial, and biomedical research, which focuses on ways to enhance the health, safety, performance and operational readiness of Navy and Marine Corps personnel and addresses their emergent medical and oral/facial problems in routine and combat operations.

RESEARCH INITIATIVES

- Integrated research focused on innovative solutions to address craniofacial injuries, dental needs and related environmental stewardship.
- Research that focuses on developing novel treatment methodologies and testing of medical devices and agents that save the lives of warfighters and extends survival one golden hour at a time.
- State-of-the-art surgical and laboratory support for research investigations.

CO: Elizabeth A. Montcalm-Smith, CAPT, MSC, USN  
XO: Barry D. Adams, CAPT MSC, USN;
Funding through BUMED, WUN G1016
Contributions to TSTC

- Provided briefings on Navy efforts to prepare for pending EPA rule which would require dental amalgam separators in dental clinics.
  - Current studies test and evaluate chairside amalgam separators for environmental contaminant removal by testing filtered effluents for metals (Hg, Cu, Ag, Sn).
  - Clinical studies are also underway to establish effective lifetime of ISO-tested, commercially available dental amalgam separators in high-volume clinics.

- Presented pilot data from air quality studies investigating the prevalence of nanoparticles in area dental laboratories (ADLs).
  - An initial survey of ADL air revealed the presence of nanoparticles.
  - Characterization by transmission electron microscopy demonstrated their composition to be consistent with known dental materials.
  - *In vitro* data suggest that material size, concentration, and composition may drive pulmonary cell toxicity, but occupational exposure risk assessments cannot be made until more data on quantities of nanoparticles in ADLs are available.

NAMRU-SA Collaborators:
- Wright Patterson AFB (Dr. Saber Hussain)
- NAMRU Dayton (LCDR Carlis Brown)
- Army Engineer Research and Development Center; Environmental Lab (Dr. Jessica Coleman; pending MOA)
Tri-Service Toxicology Consortium: Coordination Across Services
Navy and Marine Corps Public Health Center: 
Mission

Navy and Marine Corps Public Health Center (NMCPHC) provides worldwide Force Health Protection services to Naval and Joint forces in support of the National Military Strategy.

- NMCPHC Environmental Programs Department supports a wide range of environmental and medical programs, issues and customers, worldwide. Support includes providing subject matter expertise in investigating, assessing and reporting potential human health risks for hazardous substances in the environment; review of chemical and site-specific risk assessments; risk communication consultation and training; health and safety consultation for health and safety plans/accident prevention plans; and toxicological consultation for emerging contaminants and health hazard assessments. NMCPHC readily provides a multi-disciplinary public health approach to programs supported to include risk assessors; risk communicators; preventive medicine and environmental and occupational health physicians; industrial hygienists; sanitarians; epidemiologists; entomologists; radiation health specialists and toxicologists.
NMCPHC’s Recent Activities Through the Tri-Service Toxicology Consortium

- **Vapor Intrusion of Trichloroethylene:** Working with other Services to reconcile EPA and OSHA 10,000-fold difference in OELs. Provided table of different conclusions by expert panels on experiment on which EPA’s analysis depends; 3 decades of evaluation of regulatory analyses of TCE.

- **Exposures to PFCs/PFASs in water at or below EPA’s Health Advisories:** Chairing workgroup that is examining routes of exposure other than drinking, e.g., breast feeding, bathing, food (vegetables, eggs, and milk from nearby farms).

- **Review of evaluation of potential exposures to lead:** Analyses of firing ranges and submarines.

- **Discussion of ongoing Army research:** Proposed a more accurate alternative method for evaluating potential effects on male offspring of rodents (nipple retention) exposed in utero to estrogen-like chemicals.
Mission: To optimize warfighter performance through aerospace toxicology, nanoparticle, and molecular cognition research

Vision: Eliminate human mission degradation through research to support the warfighter

Research Programs
- Aerospace Toxicology
- Nanomaterials Toxicology and Effects (Nanobioeffects)
- Molecular Cognition
Toxicology:
Past AF efforts, programs & projects

- Hydrazine, propellants and hydrazine analogues
- Trichloroethylene
- Toxicity of burned composites
- Perchlorate
- Aluminum nanotoxicity for use in lighter weapons
- Jet fuel induced hearing loss
- Jet fuel toxicity - JP-4 to JP-8 conversion
- Chromate consultation
Major Current Efforts

• Develop warfighter-centric aerospace toxicology program

• Weapon system acquisition toxicology support
  – F-22, F-35, KC-46

• Toxicology consultative support for aircrew oxygen systems
  – OBOGS, bleed air: F-22, F-35, F/A-18, B-52

• Current research projects
  – Alternative jet fuels toxicity
  – Jet fuel induced hearing loss
  – Effects of exertion (high g-load) on toxicity
  – Effects of low oxygen (altitude or OBOGS air) on toxicity
Other Air Force Toxicology Entities

• Air Force School of Aerospace Medicine
  – Occupational and Environmental Health Department
    • Occupational chemistry
    • Industrial hygiene
    • Radiation health
    • Environmental risk assessment
    • Dosimetry, bioenvironmental engineering
    • ESOH service center
  – Research Department

• Air Force Civil Engineer Center
  – Environmental compliance and restoration
Collaborative Projects

• Physiologically-based Pharmacokinetic Model for Insensitive Munition Compounds
• ATSDR Toxicology Profile Review
• NAS/COT Project Review
• Toxic Load Model (Haber's Rule evaluation)
• Toxicity Evaluation & Biomarker Investigation in Rats Exposed to Burn Pit Emissions & Respirable Mid-East Sand
• Comparison of perchlorate and periodate developmental effects in amphibians
• Investigation of interactions between the human microbiome and threat chemicals
• Identification of Cytokine and mRNA Biomarkers Indicate of Neurological Effects from Exposure to Jet Fuels
• Establishment/validation of Lead PBPK Model, testing and Evaluation
• Develop Pb Air Values for Military Personnel
• Development of Occupational Exposure Levels for TCE
• Cockpit exposure reconstruction via PBPK modeling for high performance aircraft respiratory symptoms
• Cognitive effects of low-level isopropanol exposure
• Predictive toxicology toolbox build
Questions?