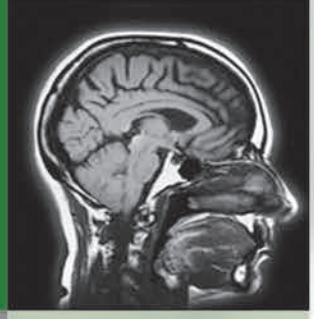

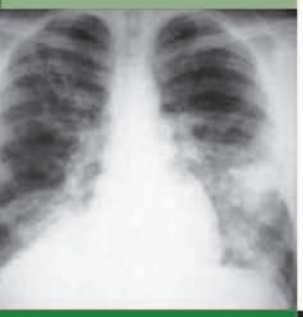
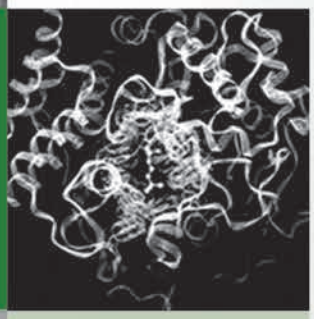

The NIH Medical Research Program Directed Against Chemical Threats

2017 Report on Research Progress and Future Directions

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2017 Report on Research Progress and Future Directions

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Institute of Allergy and Infectious Diseases

FOREWORD

Following the *NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Chemical Threats*, the National Institutes of Health (NIH) is today at the forefront of the nation's research efforts to facilitate the development of medical products that can protect the American public from the debilitating and often deadly effects of exposure to chemical threats. Where limited expertise, resources, and research activities dedicated to addressing the medical needs of civilians in response to chemical threats were available prior to 2006, there is now a substantial network of NIH-supported scientists in this field and a robust pipeline of promising medical countermeasure products.

As previously described in the *2011 Report on Research Progress and Future Directions*, the NIH Medical Research Program Directed Against Chemical Threats has raised the level of science in the field through publications in prestigious peer-reviewed scientific journals and presentations at internationally renowned conferences and workshops. The attention garnered from such activity allows NIH to recruit exceptional researchers from ancillary non-chemical defense fields into the program, bringing with them new and exciting therapeutic strategies and approaches. Consequently, NIH has created a highly collaborative research network dedicated to understanding the basic mechanisms of toxicity from chemical threats to inform the development of medical countermeasures against them. Recognizing the diversity of chemicals that have been identified as threats and their resulting toxidromes, NIH continues to draw upon the unique scientific expertise available across its many Institutes and Centers (ICs) to manage an ever-broadening portfolio of chemical defense research Centers of Excellence, cooperative agreements, grants, interagency agreements, and contracts.

As the NIH Medical Research Program Directed Against Chemical Threats program passes its 10th year, the purpose of this report is to reflect on the many research and development advancements that have been achieved thus far. The results of NIH's research and medical countermeasures development efforts are becoming increasingly evident as the overall portfolio and product pipeline matures. Highlighting this maturation is the successful transition of five potential medical countermeasures from NIH to the HHS Biomedical Advanced Research and Development Authority (BARDA) for advanced development studies since the 2011 update. Most notable among these transitioned products is the anti-convulsive drug midazolam, which is in late-stage development and poised for procurement under Project BioShield to replace diazepam in the CHEMPACK program of the Strategic National Stockpile.

Looking ahead, NIH will continue to

- Actively recruit top researchers into this field
- Foster a research infrastructure that allows for innovative ideas and approaches to understand the fundamental mechanisms of toxicity caused by chemical threat agents
- Apply this knowledge toward the development of promising therapeutics to reduce the mortality and morbidity caused by these agents

TABLE OF CONTENTS

Introduction

The general health threat posed by chemical agents has created numerous challenges for many departments and agencies across the U.S. government. Unlike infectious diseases and radiological and nuclear exposures, where a latent period may allow for prophylactic measures to be instituted prior to the manifestation of clinical symptoms, injuries from chemical exposures can occur rapidly with immediate casualties and fatalities. Many of these toxic chemicals or their precursors may be easily procured or manufactured undetected. Some of these chemicals do not even require specialized scientific expertise or knowledge for their synthesis and use. In addition, the sheer number and variety of chemicals that pose a health risk to civilians is especially daunting. Civilian chemical threats are similar to military threats and include chemical warfare agents (CWAs) such as

- Sarin
- Tabun
- Soman
- VX
- Sulfur mustard

but also include an expansive list of toxic industrial chemicals (TICs) and toxic industrial materials (TIMs), such as

- Chlorine
- Acrolein
- Aniline
- Cyanide
- Pesticides
- Hazardous acids
- Bases

As recently as the last decade, the Occupational Safety and Health Administration has identified almost 100 TICs/TIMs, while the U.S. Environmental Protection Agency lists several hundred more in its toxic release inventory.

It is impractical to develop specific medical countermeasures (MCMs) against every dangerous chemical available, so a prioritization system is necessary to focus MCM research and development efforts. As such, the U.S. Department of Homeland Security (DHS) Chemical Security Analysis Center (CSAC) was tasked with analyzing and prioritizing chemicals that have been deemed to be threats to civilians. In support of this prioritization effort, CSAC developed the Chemical Terrorism Risk Assessment (CTRA) and Chemical Infrastructure Risk Assessment (CIRA) programs, which use probabilistic risk assessments to quantify and prioritize chemical risk. More specifically, the CTRA determines the risk of a chemical attack on the public, considering

- Science of chemicals and human exposure
- Terrorist capabilities and intent
- Possibilities for different actions
- Potential for medical responses and mitigation
- General uncertainties of these factors

Similarly, the CIRA program evaluates the risk to human health from a terrorist-initiated release of a chemical from the chemical supply chain. The overall goal of these DHS programs is to estimate the risks and types of chemical terrorism attacks by specific toxidromes to help inform and improve the U.S. defense posture against such events, including the assessment of medical response capabilities after a chemical incident to identify potential gaps. The CTRA and CIRA programs are routinely updated based on new information gained from periodic modeling efforts and intelligence updates. Although the results generated by the CTRA and CIRA programs—including the list of specific toxidromes and the ranking of threat chemicals of interest—are not available for public dissemination, HHS and

NIH have used these findings to prioritize their MCM research and development strategies. The purpose of this report is to provide an update on the progress of NIH's chemical MCM research and early development program between fiscal years 2011 and 2017 and offer insight into future directions.

Deliberate Use of Toxic Chemicals Against Civilians

The events of September and October 2001 exposed the vulnerability of the United States to acts of terrorism that could employ unconventional weapons and tactics against the civilian population. Because of this heightened awareness, the U.S. government deemed the potential use of chemical, biological, radiological, and nuclear (CBRN) weapons as credible terroristic threats to Americans. Because of the devastating health effects observed both in and outside of military conflicts in recent history, compounds such as CWAs and TICs/TIMs were identified as some of the most visible and credible threats to the general public.

While CWAs were never believed to have been deployed on the battlefield during the Second World War, recent deliberate and ill-intentioned use of these compounds against both civilian and military targets is well documented. For example, organophosphorus (OP) nerve agents were used against civilians in the mid-1990s by the Japanese cult Aum Shinrikyo in Tokyo, during the Iraq-Iran War, and more recently, during the Syrian Civil War. Additionally, non-OP chemicals (sulfur mustard and chlorine) were used by the Syrian government and the militants of the Islamic State of Iraq and Syria (also known as ISIS, ISIL, or Daesh) against civilian and military targets in both Syria and Iraq.

Accidental Large-Scale Chemical Releases

In addition to the intentional release of chemicals for nefarious reasons during warfare or terrorist acts, there is also a potential for civilian exposure to these compounds due to accidental release from transportation and storage facilities during industrial accidents or natural disasters. For example, as many as 5,000 people died and more than 14,000 were injured because of a methyl isocyanate gas leak at a Union Carbide plant in Bhopal, India, in December 1984. A 2011 rail incident in Chelyabinsk, Russia, released a large bromine vapor cloud into the city of 1.1 million people. In 2015, multiple explosions at a chemical warehouse in the northern Chinese city of Tianjin released 700 tons of highly toxic substances, mainly sodium cyanide, into the air and waters in and around the city, which had a total municipal population of more than 15 million people.

Within the United States, scores of industrial and transportation accidents involving chemicals have been reported as well. For example, unintentional industrial releases of anhydrous ammonia, methyl chloride, phosgene, oleum, and chlorine have all occurred within the very recent past (details can be found on the U.S. Chemical Safety Board website). Unintentional occupational exposures are also a cause for concern. According to a 1999 release by the International Labour Organization, a specialized agency of the United Nations, approximately 275,000 deaths occur annually around the globe because of occupational exposure to hazardous substances, including TICs/TIMs. In addition, even at less toxic levels, exposure to these same substances may produce long-term adverse health effects such as impaired cardiovascular function, respiratory distress, skin lesions, and nervous system disorders.

U.S. Government Efforts in Chemical MCM Research and Development

To address the increasing potential for public health emergencies faced by the civilian population, HHS established the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) in July 2006. PHEMCE's mission is to advance national preparedness against CBRN threats and emerging infectious diseases by

centralizing the coordination of the entire U.S. government effort, including MCM research and development. Federal agencies within PHEMCE include the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR), BARDA, the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), NIH, the Department of Defense (DoD), the Department of Veterans Affairs (VA), DHS, and the U.S. Department of Agriculture (USDA). In addition to these federal agencies, PHEMCE works closely with diverse non-federal partners, including state, local, tribal, and territorial governments; public health systems; academia; private industry; and ultimately, the American people (Figure 1). PHEMCE created, and provides annual updates to, a Strategy and Implementation Plan (SIP) to help guide and coordinate efforts across agencies in real time. The goal of the PHEMCE SIP is to ensure that MCMs are available when needed. The Pandemic and All-Hazards Preparedness Act (PAHPA), enacted in December 2006, established ASPR, which manages and leads PHEMCE.

Under the broad direction of HHS, NIH undertook a leadership role in pursuing the research and early development of new and improved MCMs to prevent and/or treat mortality and serious morbidities that may result after an acute exposure to chemical threat agents. Starting in 2006, the U.S. Congress has appropriated approximately $48 million each year to NIH to execute the NIH Medical Research Program Directed Against Chemical Threats, which was developed in response to the NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Chemical Threats. This program is directed by the Chemical Countermeasures Research Program (CCRP) within the National Institute of Allergy and Infectious Diseases (NIAID). The CCRP has two important goals. First, it supports basic research to understand the toxicology of chemical threat agents, so that novel therapeutic targets and approaches can be identified. In this regard, the program serves as a science and technology base for the larger federal research effort. Second, the CCRP supports more mature projects with promising lead MCM compounds that may be eligible for further development and regulatory approval. Under this second goal, NIH aims to transition such lead products to other entities that support advanced research and development studies. One such entity and key NIH partner is BARDA (**www.phe.gov/ABOUT/BARDA/**), which was established within the Office of the ASPR by the PAHPA in 2006.

The NIAID/NIH Chemical Countermeasures Research Program (CCRP)

The CCRP is part of the larger NIH biodefense research program coordinated by NIAID, which also includes research and development of MCMs against biological, radiological, and nuclear threats. The overarching goal of the CCRP is to integrate cutting-edge research with the latest technological advances in science and medicine to enhance the nation's medical response capabilities during public health emergencies involving the release of chemical threat agents. The CCRP is a collaborative network of academic, industry, and federal laboratories. It leverages the expertise of multiple NIH ICs to manage the research and early development of MCMs that could prevent lethality and/or treat injuries resulting from toxic chemical exposure.

The CCRP supports a research infrastructure comprising contracts and interagency agreements (IAAs) with the DoD and HHS in addition to an extensive NIH-wide research grant program called the Countermeasures Against Chemical Threats (CounterACT) program. The CounterACT program is guided by the National Institute of Neurological Disorders and Stroke under the oversight of NIAID. The National Eye Institute, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institute of Environmental Health

Sciences (NIEHS), the National Library of Medicine, and the National Institute on Drug Abuse all participate in the CounterACT program.

One aim of the CCRP is to understand the pathology of chemical exposures and develop specific medical treatments under the overall PHEMCE strategy for chemical threats. As such, the multidisciplinary expertise available through partnering with these NIH Institutes is critical to the CCRP's success because the chemical threats of concern target many aspects of normal human physiology and function (e.g., neurological, pulmonary, ocular, skin). The expertise is also critical for understanding the underlying injury processes resulting from chemical agents, such as the toxicological effects of chemical compounds and their effects on various stages of human growth and development, including *in utero*, pediatric, and geriatric.

The CCRP supports the development of MCMs that can be used to reduce mortality or serious morbidity during an intended or accidental emergency involving those chemicals that have been identified as threats by the DHS CTRA and CIRA programs. A focus of research supported under this program is to understand the pathophysiology associated with acute exposure to toxic chemicals and to identify compounds that are therapeutically effective when administered after exposure has already occurred (post-exposure efficacy). Although those compounds that are only effective if administered prior to a chemical insult (prophylaxis efficacy) could potentially be used for emergency first responders and receivers, the focus of the CCRP is identifying post-exposure therapeutics.

The general scope of supported research includes mechanistic research to identify potential targets for therapeutic development and/or intervention, e.g., research on the molecular mechanisms of toxicity for identifying novel drug targets and/or biomarkers. For known targets, the program supports the creation and development of screening assays that must be validated with appropriate pharmacology, biological activity, and other factors that increase the likelihood that candidate therapeutics emerging from the *in vitro* screening activity will be effective *in vivo*. Creating and validating animal models that include toxicity outcome measures predictive of human outcomes and that assess lethality and serious near- and long-term sublethal morbidities is a primary goal.

THE NIAID/NIH CCRP Research Infrastructure

From its inception, the CCRP has sought to both use the expertise of researchers already active in the CWA field and engage the large cadre of NIH-funded investigators in scientific areas that are relevant to this field. For example, if untreated, chemical nerve agents can cause seizures and other neuropathological sequelae, conditions that share molecular mechanisms and phenotypes with neurological illnesses such as epilepsy and stroke. These disorders are research areas that NIH has supported for decades, and this has provided an unprecedented opportunity for NIH to engage researchers from these fields. To accomplish this goal, the CCRP continues to convene an annual research symposium that gives supported researchers the opportunity to learn about recent advances in the field and potential avenues for fruitful collaborations. Similarly, to engage those scientists not already in the field, NIH supports ad hoc expert panels and workshops as necessary (Table 1).

The CCRP uses multiple funding mechanisms such as contracts, IAAs, and grants to support basic, translational, and clinical research aimed at the discovery and identification of new and improved MCMs against chemical threat agents, with the goal of shepherding them from proof-of-principle efficacy through advanced development and regulatory approval. More specifically, the CCRP supports these research efforts through funding for specialized center cooperative

agreements (U54), research project cooperative agreements (U01), exploratory/developmental grants (R21), small business innovation research (SBIR) grants (Table 2), and IAAs (Table 3). Since 2011, the CCRP has supported a network of

- Milestone-driven cooperative research grants composed of 6 U54 Research Centers of Excellence (Table 4) and 41 U01 individual research projects
- Fifty R21 small exploratory/developmental research projects
- Forty-six interagency agreement research projects with the DoD

In addition to the numerous research projects supported by the CCRP between 2011 and 2017, several NIH-supported core resources and facilities were established or continued to provide additional access and collaboration opportunities, such as

- **The CounterACT Efficacy Research Facility (CERF)**, established in 2010, continues to conduct studies in support of NIH-supported investigators, as well as research initiated by the U.S. government and conducted under direct NIH oversight and collaboration with other U.S. government partners. The facility also serves to increase the capacity for conducting studies with chemical agents that require special surety facilities. The facility has a long-standing partnership with the DoD. Between fiscal years 2011 and 2017, the CERF conducted 28 studies, including the development of large animal (swine) models of cyanide and sulfur mustard intoxication that were subsequently transitioned to BARDA. Of note, the swine cyanide intoxication model was used to demonstrate that the intramuscular administration of sodium nitrite and sodium thiosulfate (both FDA-approved as intravenous therapies for cyanide poisoning) can effectively prevent lethality. These and other CERF-supported studies have resulted in 38 presentations at national and international scientific conferences and 16 peer-reviewed publications.
- **The CounterACT Preclinical Development Facility (CPDF)**, established in 2006, continues to enable investigators to conduct preclinical studies needed for drug discovery and development and, ultimately, FDA approval. Studies approved by NIH are performed at no cost to the researcher. Between fiscal years 2011 and 2017, the CPDF was used by more than two dozen CCRP-funded researchers to support more than 40 preclinical studies and activities, such as good manufacturing practice (GMP) production of lead compound(s).
- **The CounterACT Neurotherapeutics Screening (CNS) program**, established in 2015, gives prospective investigators the opportunity to submit compounds to be evaluated for both anticonvulsive and neuroprotective properties against OP-induced seizures using rigorously validated animal models. This medium-throughput screening program works closely with the DoD at the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD) to test potential therapies against the threat chemical soman (GD), a CWA that cannot be used outside of a few federal laboratories and contract research organizations. The primary goal is to identify MCMs that can mitigate benzodiazepine-refractory nerve agent-induced *status epilepticus* (SE). CNS studies approved by NIH are also performed at no cost to the applicant researcher. Since its inception in 2015, the CNS has evaluated a dozen novel or commercially available compounds, including the FDA-approved and marketed sedative-analgesic Precedex (Dexmedetomidine hydrochloride). As an adjunct to midazolam in the screening models, this compound was the first to terminate GD-induced SE successfully when administered up to 40 minutes after initial onset of seizure activity.

Scientific Advances Between 2011 and 2017

The CCRP supports not only the discovery of novel compounds with requisite therapeutic activity and acceptable safety profiles, but also "repurposing"—research to expand the marketed indications of FDA-approved therapeutics for chemical defense indications. Additionally, CCRP supports studies to identify alternate routes of administration amenable for mass casualty scenarios for both new and already marketed therapies. The goal of these efforts is to develop products that would be safe and effective, as well as readily available and easy to administer during a mass casualty event (e.g., intramuscular injection). Although the program supports research of antidotes that are specific to a chemical agent, it also aims to develop countermeasures that can be effective against the acute effects and pathologies common to multiple chemical threat agents (e.g., toxidrome-based therapies). This latter approach would allow for the development of a therapy that can be used to treat injuries caused by a spectrum of chemical threats with common mechanisms and pathologies, thus potentially simplifying access to care. Special consideration is given to research relevant to populations who are particularly vulnerable, including the young, the elderly, pregnant women, and individuals with preexisting medical conditions. Children and pregnant women, for example, have been shown to be much more sensitive to the toxicity of some CWAs and thus may require specialized medical management after exposure. Consequently, animal models and studies that address these vulnerabilities, as well as long-term effects after an acute exposure, are of great interest.

The following sections briefly highlight recent advancements in the CCRP portfolio, including development transitions to BARDA (Table 5) since the publication of the last progress report in 2011. Consistent with the goal of enhancing public preparedness and medical response capabilities to chemical threat agents, the focus of these sections will be on outcomes (e.g., identification of toxicity, potential therapeutic product(s)).

Chemicals Affecting the Nervous System

A number of the chemical threats identified by DHS are known to target the nervous system. These chemicals include cholinergic agents that can induce seizures commonly resulting in neuropathology and, in the longer term, adverse neurological and behavioral sequalae. From the civilian perspective, cholinergic-based chemical threats include classic CWA nerve agents as well as OP pesticides such as chlorpyrifos, phorate, paraoxon, and disulfoton. Also included here are carbamate pesticides such as aldicarb and methomyl. The primary mechanism of toxicity exerted by OP and carbamate poisons is anti-cholinesterase (anti-ChE) activity via inhibition of ChE enzymes, especially the neurotransmitter acetylcholinesterase (AChE). The inhibition of AChE results in increased acetylcholine (ACh) levels in the synapses of the central and peripheral nervous systems. If this increase is left uncontrolled, clinical manifestations of intoxication can occur quickly, including miosis, fasciculations, respiratory distress, seizures, convulsions, increased secretions, and death. While the mechanism of toxicity of CWAs and carbamate and OP pesticides is similar, the relative potencies can be radically different. NIH continues to support research aimed at mitigating the resulting cholinergic toxicity. Since 2011, the neurological threat component of the overall NIH portfolio has included 2 U54 centers—located at USAMRICD and the University of California at Davis—18 U01 projects, 25 small exploratory/translational R21 projects, 1 SBIR grant, and 21 IAA research projects with the DoD USAMRICD focusing on the toxic effect after exposure to chemical warfare nerve agents (Table 6). These projects have taken many different antidotal and symptom-based therapeutic approaches.

The current FDA-approved antidotal approach for anti-ChE intoxication in the United States is the use of the competitive muscarinic receptor antagonist atropine to mitigate the hyperstimulation of peripheral postsynaptic targets and the AChE oxime reactivator pralidoxime chloride (2-PAM Cl) to augment OP dissociation from and reactivation of inhibited AChE. The combination of these two therapeutic strategies aims to reduce the hyperstimulation of parasympathetic nerves that results from the overaccumulation of ACh. The U.S. government fields these two drugs within a single two-chambered, self-propelled syringe via a common needle intramuscular injection delivery system, the Antidote Treatment-Nerve Agent, Auto-Injector (ATNAA), which is mainly for military use, and the DuoDote Auto-Injector, which is labeled for civilian application.

Although 2-PAM Cl is efficacious to some extent against sarin and VX, a broader spectrum of activity against the various OP nerve agents, pesticides, and carbamates is desired. Additionally, 2-PAM CI has minimal efficacy within the central nervous system due to poor penetration across the blood-brain barrier (BBB). Consequently, the CCRP initiated multiple studies through the CERF program, in close collaboration with the DoD and BARDA, to identify oxime candidates with broader efficacy than 2-PAM Cl. The overall objective was to compare the efficacy of several currently fielded and a select few promising novel AChE oxime reactivators against OP CWAs and pesticides under strict standardized and rigorous unbiased experimental conditions. In general, the oxime that offered the best protection against the spectrum of OP chemicals evaluated was MMB4 DMS, which is currently under advanced development by the DoD as a replacement for 2-PAM Cl. Other NIH-supported research involving scientists from USAMRICD, the University of California at San Diego, the University of Mississippi, and Wright State University, among others, has made remarkable advances, identifying novel oxime reactivators with improved efficacy, capacity to cross the BBB (and thus centrally protective), or a combination of both. Concurrent with these developments, NIH-supported researchers have also focused on alternate antidotal approaches, e.g., enzyme-mediated or -assisted therapy, specifically with butyrylcholinesterase (BChE), paraoxonase-1 (PON1), and organophosphate hydrolase (OPH). Through NIH support, recent technological advances have resulted in successes in improving the circulatory half-life of these enzymes and/or enhancing their natural ability to break down and detoxify CWAs even when administered minutes after CWA exposure.

Because prolonged, uncontrolled seizures and/or SE are common symptoms of cholinergic poisoning, therapeutic-based cessation of this effect represents another potential treatment strategy. As such, NIH has continued to recruit senior neuroscientists, especially those in the field of epilepsy research, to the CCRP. As a result of this outreach effort, a number of compounds currently under study as potential treatments for neurological disorders such as seizure, stroke, and traumatic brain injury have been evaluated for their capacity to treat chemically induced SE. Some of these compounds, including tezampanel and midazolam, have demonstrated good anticonvulsive efficacy in terminating seizures induced by OP pesticides, CWAs, or both, resulting in decreased neuropathology. In addition to these findings, other CCRP-supported projects have identified potential adjuncts that can be administered with the current standard of care, i.e., atropine and 2-PAM, specifically to reduce the neuropathology that commonly occurs after termination of seizure activity. Examples of efficacious adjuncts include both natural and synthetic neurosteroids such as allopregnanolone and ganaxolone as well as the sedative dexmedetomidine.

The CounterACT grant program previously supported a double-blind, randomized clinical trial to compare a novel midazolam intramuscular

auto-injector, which could allow for the intramuscular delivery of midazolam to patients before they arrive at the hospital, against intravenous lorazepam, another treatment for seizures in humans. This trial, known as Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART; NCT00809146), used the same drug and auto-injector device proposed for use in humans exposed to OPs. The goal was to determine whether the new therapy approach (midazolam intramuscular) was as effective in terminating SE in a prehospital setting as the standard of care (lorazepam intravenous). The results of this CCRP-supported study indicated that not only was midazolam intramuscular as efficacious as lorazepam intravenous, it was faster acting and more consistently effective. The results of this study not only supported the transition of this MCM to BARDA in 2013 (Table 5), but were essential for the 2017 New Drug Application (NDA) to the FDA. It is anticipated that this product would be procured by the U.S. government for the Strategic National Stockpile (SNS) under Project BioShield if the NDA is approved. Other studies are ongoing to develop alternate delivery platforms, such as intranasal, for both novel and marketed compounds to mitigate acute neurological effects after chemical exposure. In addition, the CounterACT grant program is also collaborating with the NIEHS National Toxicology Program to develop a systematic review of the evidence for long-term neurological health effects after acute sarin exposure, i.e., what happens after the initial seizures have been controlled.

Finally, in addition to cholinergic-based neurological chemical threats, the NIH portfolio has recently expanded to include emerging chemical threats that interfere with the physiological activity of other neurotransmitters, such as gamma-aminobutyric acid (GABA) and glycine. These threats are commonly referred to as convulsive agents and include tetramethylenedisulfotetramine (TETS or tetramine), picrotoxin, and strychnine. Although the current research effort on these chemicals is comparatively smaller, substantial progress has already been made in understanding their mode of intoxication and evaluating the efficacy of potential MCMs against them.

Chemicals Affecting the Respiratory Tract

Many of the pulmonary chemical threat agents identified by the DHS CTRA program are widely available and easily accessible TICs/TIMs. Since 2011, the NIH portfolio for this threat class has included 2 U54 centers, 14 individual U01 projects, 11 small exploratory/translational R21 projects, and 7 large interagency agreement research projects with the DoD USAMRICD (Table 7). This threat category represents the largest gap in the overall chemical defense research portfolio because of the sheer number of compounds that affect the respiratory system, and it is a gap that the NIH program has sought to fill. The primary toxicity of this class of chemical is damage to the pulmonary/respiratory system that can be severely debilitating and even life-threatening. Depending on the dose and duration of exposure, all of the identified pulmonary threat chemicals have the capacity to irritate and damage the lining of the respiratory tract from the points of entry, i.e., nose and mouth, to the alveoli, resulting in acute lung injury. Nonetheless, because the sheer number of pulmonary TICs/TIMs is large and varied, these inhalational poisons are further divided into those that, in the acute setting, primarily affect either the upper or lower airways of the pulmonary system. Examples of upper pulmonary-specific threats include anhydrous and aqueous ammonia, oleum, aniline, diborane, and sulfur dioxide. Lower pulmonary-specific chemicals include chlorine, phosphine, phosgene, chloropicrin, and methyl isocyanate. Unfortunately, no therapeutic treatment has been approved to treat chemically induced injuries to either the upper or lower respiratory systems specifically. Medical intervention has primarily focused on supportive

care, e.g., oxygen supplementation via ventilator support to induce positive airway pressure, potential off-label use of available bronchodilators to treat bronchospasm, and anti-inflammatory drugs to mitigate edema.

Because of the high number of TICs/TIMs that specifically target the pulmonary system, NIH supports a broad-spectrum therapeutic development approach that emphasizes treating common symptoms, pathways, and/or pathologies of injury rather than developing specific antidotes for individual chemicals. Some of the symptoms of chemically induced pulmonary injuries overlap to a certain degree with some pulmonary diseases and disorders including

- Asthma
- Acute respiratory distress syndrome (ARDS)
- Bleomycin toxicity
- Viral-/bacterial-based respiratory infections

Recognizing this overlap, the CCRP made a concerted effort to recruit pulmonary toxicologists and pulmonologists from research and medical institutions across the country into this field. The aim of this approach was to identify common symptoms and pathology progression between chemical and nonchemical pulmonary injuries with the possibility of using marketed medical products for a chemical countermeasure-based indication.

As a result of this research strategy, NIH-supported researchers have identified a number of potential therapies for pulmonary threat agents that may be effective in reducing the overall inflammatory response, promoting tissue healing, and preventing the onset of pulmonary edema or secondary inflammation to prevent chronic scarring and airway narrowing and/or obstruction. NIH-supported research extends from basic studies to identify genes and pathways potentially influenced by exposure to the development of animal models to replicate the *in vivo* response after exposure. Establishing relevant animal models, ranging from small rodent models to recently developed rabbit, swine, and goat models, subsequently allows for the tentative identification and validation of the putative mechanism of injury and possible therapeutic targets and therapies. Because of these efforts, a number of compounds, some already approved for other indications, have been identified and evaluated as potential MCMs. These compounds include the following:

- Ascorbate
- Nitrite
- Rolipram
- Triptolide
- Budesonide
- Mometasone
- Glutathione
- Trolox (vitamin E analog)
- AEOL 10150
- Heparin
- Transient receptor potential ankyrin 1 (TRPA-1) channel antagonists
- Various β2-agonists
- Hydralazine
- Anti-fibrotic agents, such as tissue plasminogen activator (tPA; alteplase)

Although the exact mechanism of how these compounds afford potential protection is still under investigation, in general, these compounds exhibit anti-inflammatory, anti-oxidative, and antifibrinolytic properties, which help to prevent and treat pulmonary inflammation, edema, airway hyperactivity and hyperplasia, and fibrosis to reduce morbidity and mortality.

To treat vesicant-induced pulmonary injuries, identified therapeutic candidates include pentoxifylline to attenuate mustard-induced acute lung injury, oxidative stress, and inflammation; recombinant tissue factor pathway inhibitor (TFPI) and the previously mentioned tPA to diminish airway obstructive fibrin-containing casts; aminoguanidine to inhibit nitric oxide production; and AEOL 10150 to mitigate the resultant oxidative stress processes in the lungs. Of these promising products, the clot-busting drug alteplase (tPA) was transitioned from NIH to BARDA in 2015. Under advanced development through BARDA, the drug will be further evaluated as a potential treatment for acute respiratory distress resulting from inhaled sulfur mustard (Table 5).

In 2016, NIH transitioned a potential antidote (R-107) to BARDA for advanced development. R-107 was developed to treat the life-threatening effects of chlorine inhalation (under development by Radikal Therapeutics). This transition was soon followed by an award to GlaxoSmithKline in 2017 to develop transient receptor potential cation channel subfamily V member 4 (TRPV4) channel blockers as a treatment for chlorine inhalation injuries. These two product transitions represent an important step forward in preparedness against chlorine inhalation (Table 5).

Chemicals Affecting the Skin, Eyes, and Mucous Membranes

Vesicating agents or vesicants can cause moderate to debilitating injuries and pain to the eyes, skins, and mucous membranes. Chemicals in this class include

- Sulfur/nitrogen mustard
- Lewisite
- Phosgene oxime
- Various arsine compounds such as ethyldichloroarsine and diphenylcyanoarsine

The primary modes of exposure to these chemicals are inhalation, ingestion, dermal, and ocular. Depending on the dose, route, and duration of exposure, toxic symptoms can range in varying degrees of bronchospasm, dyspnea, pulmonary edema, bronchitis, blister formation, dermal or ocular burns, and immuno- and bone marrow suppression. Although exposure to vesicants is not often lethal, these threat chemicals are nonetheless of interest to the U.S. government because of both short- and long-term effects of poisoning. In certain instances, the physical effects of injury may not be readily apparent until several hours after initial exposure, which complicates the potential for early diagnosis (based only on clinical signs and symptoms) and medical intervention. Since 2011, the NIH portfolio for this threat class has included one U54 Center of Excellence at Rutgers University, four individual U01 projects, four small exploratory/translational R21 projects, and seven IAA research projects with the DoD USAMRICD focusing on the toxic effect of sulfur mustard (Table 8).

The only FDA-approved therapy for this class of chemicals to date is dimercaprol (British anti-Lewisite or BAL). This heavy metal-chelating compound has been shown to decrease the severity of skin and ocular lesions after Lewisite exposure. However, in addition to the possible toxic effects of BAL itself, its effectiveness is greatest if administered immediately after exposure, which makes this therapy less suitable in a civilian post-exposure scenario. Aside from BAL, the current therapeutic approach is mainly supportive:

- Management of symptoms with off-label use of available antibiotics to prevent secondary infections
- Steroids and anti-inflammatory drugs to limit the inflammatory responses
- Antioxidants to mitigate oxidative stress
- Skin debridement to expedite the healing process after vesicant exposure

Consequently, there is an urgency to develop MCMs against these chemical threats.

In recent years, NIH-supported researchers have developed a number of animal models demonstrating the toxic effects of various vesicants. These models have sought to replicate the dermal, ocular, and respiratory toxicities of some of these chemicals. As a direct result of these animal models, several potential drug targets have been discovered, which has led to the identification and evaluation of numerous potential therapies.

For example, efforts to identify therapeutics to treat the dermal toxicity induced by vesicating agents have identified several promising candidates, including

- Capsaicin, diclofenac, and clobetasol, which have shown varying degrees of success in reducing lesion contracture, increasing barrier function, and healing
- 25-hydroxyvitamin D3 (25(OH)D), which was able to suppress macrophage-mediated inducible nitric oxide synthase (iNOS) production, leading to mitigation of local skin destruction, enhanced tissue repair, protection from bone marrow depletion, and rescue from severe precipitous wasting
- Silibinin, which decreased mustard-induced increases in epidermal thickening, dead and denuded epidermis, parakeratosis, and microvesication
- AEOL 10150, which reduced skin bi-fold and epidermal thickness, myeloperoxidase activity, and DNA oxidation in mice after exposure to the chemical threat

From concurrent research to identify countermeasures to treat and/or prevent ocular injuries induced by vesicants, compounds such as silibinin (a natural flavonoid), dexamethasone (an anti-inflammatory steroid), and doxycycline (an antibiotic and matrix metalloproteinase-9 [MMP-9] inhibitor) have demonstrated varying degrees of efficacy to reverse the resultant epithelial thickening, microbullae formation, apoptotic cell death, and MMP-9 elevation.

Chemicals Affecting Cellular Respiration

Metabolic poisons are chemicals that specifically target and interfere with normal cellular respiration. Chemicals in this threat class are also referred to as "blood" agents by the DHS CTRA and include compounds such as cyanogen chloride, hydrogen/potassium cyanide, hydrogen sulfide, acrylonitrile, sodium azide, methanethiol, and sodium fluoroacetate. The most common routes of toxic exposure for this group of threat agents are inhalation and ingestion. These chemicals interfere with cellular respiration, which can lead to the inhibition of the intracellular use of oxygen, thereby preventing the normal production of energy critical for cellular functioning and survival. All of the body's physiological functions can be seriously affected by these poisons, especially those activities with the highest needs for oxygen and energy, such as the functions of the central nervous and cardiovascular systems. Consequently, an acute exposure to high levels of these chemicals can rapidly lead to seizures, respiratory distress, cardiac failure, and death. As such, immediate recognition of the clinical symptoms of intoxication is of utmost importance, as is the need for an antidote that is easy to administer, fast-acting, and safe (even if given absent assurance of exposure).

There are currently two FDA-approved therapies for a chemical in this class of poisons: Cyanokit and Nithiodote. Both products are only approved for cyanide intoxication (actual and suspected) and involve extremely close monitoring of patients to prevent adverse effects. Another drawback of the two products is the need to administer them intravenously, a delivery method that is not amenable for a mass casualty scenario. Given these limitations, more research is needed

to develop broader acting therapies that are also amenable to mass casualty use. Also needed are additional animal models of exposure that can be used across chemicals within this class. Since 2011, research on this class of threat chemicals has included 1 U54 Center of Excellence at Brigham and Women's Hospital and Harvard University, 5 individual U01 projects, 10 small exploratory/translational R21 projects, 2 SBIR grants, and 11 IAA research projects with the DoD USAMRICD (Table 9).

Through the CCRP, several small and large animal models of intoxication by metabolic poisons have been developed and validated during the past five years. *In vivo* models have ranged from small animals, such as rodents and rabbits, to large animals that are more relevant to humans, such as swine and sheep. Using these models, a few compounds have demonstrated efficacy in promoting overall survival after cyanide exposure. These promising compounds include the following:

- Dimethyl trisulfide (DMTS)
- Methylene blue
- Cobinamide
- Methemoglobin
- Sodium nitrite
- Sulfanegen

The mechanistic action of most of the identified therapies is to either scavenge or detoxify the target chemical threat by metabolism while the chemical insult is still in circulation and before cellular respiration is severely affected. When it is not possible to remove the chemical threat from the circulatory system, attempts to mitigate the potential chronic or longer term neurological impacts of intoxication have identified carnosic acid, a pro-electrophilic compound, as a potentially viable therapy (for cyanide poisoning). Carnosic acid is hypothesized to protect the brain by upregulating central antioxidant enzymes to reduce the neuronal cell loss that commonly occurs after seizure activity. Although most of the efficacy demonstrated to date has been for either hydrogen sulfide or cyanide, the vitamin B12 analog cobinamide has been shown to enhance survival after poisoning by both of these chemicals. This observation raises the possibility that a "one compound for multiple chemical threats" therapy may be possible.

Future Directions

Although the NIH Medical Research Program Directed Against Chemical Threats only began in 2006, it has made tremendous progress since the publication of the previous progress update in 2011. For example, a number of promising potential MCMs have been discovered and even more models of chemical threat poisoning have been developed. At the forefront of these accomplishments is the previously mentioned RAMPART study (winner of the 2013 David Sackett Trial of the Year Award), which was conducted in collaboration with several key stakeholders, including academic researchers, industry (Meridian Medical Technologies, a Pfizer company), and federal government partners (HHS and DoD). The success of this study led to the award of a $60 million BARDA contract to develop midazolam auto-injectors as a replacement for the diazepam auto-injectors currently in the SNS as an MCM against nerve-agent exposure. Additionally, several other highly promising products have also rapidly advanced through the CCRP pipeline and have transitioned to BARDA for further advanced development support (Table 5). NIH-supported researchers have made great strides expanding the knowledge base in the chemical threats field. Many expert researchers have been recruited to the program, which has led to invaluable contributions and advancements. Advances in the biological and toxicological understanding of many of the threat chemicals of interest led to more than 600 peer-reviewed publications between 2011 and 2017 (Figure 2) and more than 1,200 peer-reviewed publications since

the inception of the NIH program in 2006. Additionally, NIH-supported researchers in chemical defense have made countless presentations at national and international scientific conferences.

Despite the aforementioned successes, much more needs to be accomplished in light of the ever-increasing threat of terrorism, warfare, and storage/transportation accidents involving civilians and chemicals. Developing MCMs to protect civilians against chemical threats is a daunting task. For example, the majority of NIH-supported projects are performed by academic laboratories that often do not possess the necessary resources and expertise (e.g., regulatory and manufacturing) necessary to bring a potential therapy from the bench to the bedside. As such, it is often critical that NIH-supported researchers partner with the pharmaceutical or biotechnology sector to leverage their respective resources and expertise to develop the potential countermeasure further. NIH strongly encourages its academic researchers to form these collaborative partnerships with industry as early in the research and development pipeline as possible. These drug development partnerships are especially important because it is neither ethical nor feasible to perform human clinical trials to establish the efficacy of proposed therapeutic products for treating injuries resulting from exposure to chemical threats. As such, a keen understanding of the FDA Animal Rule is necessary to formulate the most appropriate development and regulatory strategy for potential MCMs. To date, about a dozen compounds have been approved under the Animal Rule for all CBRN threats.

Lastly, the sheer number of chemicals that pose a legitimate and serious threat to civilians is overwhelming and continues to grow as additional compounds are identified by DHS. For example, recent additions to the list of chemical threats of interest include pharmaceutical-based agents, such as synthetic opioids, and anticoagulants like brodifacoum. The civilian-directed research and development effort must focus on medical intervention during and after an acute exposure as well as needed long-term care. This long-term response is especially important where acute mortality is prevented but chronic morbidity remains, particularly in more vulnerable subpopulations, such as children, seniors, and pregnant women. Consequently, the continued expansion of the list of chemical threats, the diversity of the general population, and the pressing need to address both acute and long-term medical care all present significant challenges to the chemical countermeasure research and development endeavor, which the CCRP must continue to address going forward. As such, it is imperative that the CCRP continue to recruit top scientists and innovation into this field, while sustaining a highly collaborative relationship both within NIH across the partner ICs and with the other PHEMCE partners, particularly BARDA, FDA, and DoD.

Table 1: Key Workshops and Expert Panels on Chemical Threats and Medical Countermeasures

Year	Title	Location
2012	6th Annual NIH Countermeasures Against Chemical Threats (CounterACT) Network Research Symposium	San Francisco, California
2013	7th Annual NIH Countermeasures Against Chemical Threats (CounterACT) Network Research Symposium	Bethesda, Maryland
2014	8th Annual NIH Countermeasures Against Chemical Threats (CounterACT) Network Research Symposium	Denver, Colorado
2014	Neurological Effects After Chemical Nerve Agent Exposures Workshop	Rockville, Maryland
2015	9th Annual NIH Countermeasures Against Chemical Threats (CounterACT) Network Research Symposium	Manhattan, New York
2016	10th Annual NIH Countermeasures Against Chemical Threats (CounterACT) Network Research Symposium	Davis, California
2017	11th Annual NIH Countermeasures Against Chemical Threats (CounterACT) Network Research Symposium	Boston, Massachusetts
2017	NIH Expert Panel Workshop on Cyanide	Boston, Massachusetts

Table 2: NIH Grant Funding Opportunity Announcements Soliciting Research Proposals

Year of Release	Announcement Title
2012	
PA-12-088	PHS 2012-02 Omnibus Solicitation of the NIH, CDC, FDA, and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44])
PA-12-089	PHS 2012-02 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42])
2013	
PAR-13-005	Countermeasures Against Chemical Threats (CounterACT) Exploratory/Developmental Projects in Translational Research (R21)
PAR-13-208	Countermeasures Against Chemical Threats (CounterACT) Cooperative Research Projects (U01)
PA-13-088	PHS 2013-02 Omnibus Solicitation of the NIH, CDC, FDA, and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44])
PA-13-089	PHS 2013-02 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42])
2014	
PA-14-071	PHS 2014-02 Omnibus Solicitation of the NIH, CDC, FDA and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44])
PA-14-072	PHS 2014-02 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42])

Year of Release	Announcement Title
2015	
PAR-15-146	Countermeasures Against Chemical Threats (CounterACT) Research Centers of Excellence (U54)
PAR-15-315	Countermeasures Against Chemical Threats (CounterACT) Exploratory/Developmental Projects in Translational Research (R21)
PA-15-269	PHS 2015-02 Omnibus Solicitation of the NIH, CDC, FDA, and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44])
PA-15-270	PHS 2015-02 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42])
2016	
PAR-16-128	Countermeasures Against Chemical Threats (CounterACT): Optimization of Therapeutic Lead Compounds (U01)
PAR-16-129	Countermeasures Against Chemical Threats (CounterACT): Identification of Therapeutic Lead Compounds (U01)
PAR-16-329	Countermeasures Against Chemical Threats (CounterACT) Research Centers of Excellence (U54)
PAR-16-330	Countermeasures Against Chemical Threats (CounterACT): Identification of Therapeutic Lead Compounds (U01)
PAR-16-331	Countermeasures Against Chemical Threats (CounterACT): Optimization of Therapeutic Lead Compounds (U01)
PA-16-302	PHS 2016-02 Omnibus Solicitation of the NIH, CDC, FDA, and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44])
PA-16-303	PHS 2016-02 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42])
2017	
PA-17-302	PHS 2017-02 Omnibus Solicitation of the NIH, CDC, FDA, and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44])
PA-17-303	PHS 2017-02 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42])

Table 3: IAAs and Contracts

Neurological Research: Funded Through the "Chemicals Affecting the Nervous System – Anticonvulsants/Neuroprotectants" Program	
2012–2013	AOD12058-001-00000: Received by DoD USAMRICD
2013–2014	AOD13014-001-00000: Received by DoD USAMRICD
2014–2015	AOD14018-001-00000: Received by DoD USAMRICD
2015–2016	AOD15015-001-00000: Received by DoD USAMRICD
2016–2017	AOD16024-001-00000: Received by DoD USAMRICD
Cyanide Research: Funded Through the "Cyanide Diagnostics and Efficacy Testing of Next Generation Cyanide Antidotes" Program	
2012–2013	AOD12060-001-00000: Received by DoD USAMRICD
2013–2014	AOD13016-001-00000: Received by DoD USAMRICD
2014–2015	AOD14020-001-00000: Received by DoD USAMRICD
2015–2016	AOD15017-001-00000: Received by DoD USAMRICD
2016–2017	AOD16026-001-00000: Received by DoD USAMRICD
Pulmonary Research: Funded Through the "Chemicals Affecting the Respiratory Tract – Pulmonary Toxicant Gases" Program	
2012–2013	AOD12061-001-00000: Received by DoD USAMRICD
2013–2014	AOD13017-001-00000: Received by DoD USAMRICD
2014–2015	AOD14021-001-00000: Received by DoD USAMRICD
2015–2016	AOD15018-001-00000: Received by DoD USAMRICD
2016–2017	AOD16027-001-00000: Received by DoD USAMRICD
Vesicant Research: Funded Through the "Chemicals Affecting the Skin, Eyes, and Mucous Membranes – Toxic Vesicants and Industrial Chemicals" Program	
2012–2013	AOD12059-001-00000: Received by DoD USAMRICD
2013–2014	AOD13015-001-00000: Received by DoD USAMRICD
2014–2015	AOD14019-001-00000: Received by DoD USAMRICD
2015–2016	AOD15016-001-00000: Received by DoD USAMRICD
2016–2017	AOD16025-001-00000: Received by DoD USAMRICD
Chemical Countermeasures: Studies To Support Countermeasures for Highly Toxic Materials Including Chemical Agents and Toxins	
2013	AOD13013-001-00000: Received by DoD Defense Technical Information Center
Chemical Countermeasures Collaboration	
2011	Y1-OD-1159-01: Received by DoD Edgewood Chemical and Biological Center (ECBC)

CounterACT Efficacy Research Facility (CERF)	
2016–2021	AOD16029-001-00000: Received by HHS Program Support Center (PSC)
2017	AOD17032-001-00000: Received by HHS PSC
CounterACT Preclinical Development Facility (CPDF)	
2012–2017	HHSN271200623691C: Received by SRI International

Table 4: 2011–2017 CounterACT Centers of Excellence and Primary Investigators

Title	Principal Investigator	Institution	Project Identifier	Threat Area(s)
Center for Catalytic Bioscavenger Medical Defense Research II: Discovery, Formulation, and Preclinical Evaluation	Cerasoli, D.M.	USAMRICD	U54 NS058183	Neurological
Rutgers University CounterACT Research Center of Excellence	Laskin, J.D.	Rutgers Biomedical and Health Sciences School of Public Health	U54 AR055073	Vesicant
Novel Anticonvulsant and Neuroprotective Therapies for TETS and OP Intoxication	Lein, P.J.	University of California, Davis	U54 NS079202	Neurological
A Discovery and Development Pipeline for Cyanide Countermeasures	MaCrae, C.A.	Brigham and Women's Hospital	U54 NS079201	Cellular Respiration
Novel Therapeutics for Vesicants and Toxic Inhaled Chemicals	White, C.W.	University of Colorado, Denver	U54 ES015678	Vesicant and Pulmonary
Development of Antidotes for Toxic Gases	White, C.W.	University of Colorado, Denver	U54 ES027698	Pulmonary

Table 5: NIH Advanced Development Transitions to BARDA Since 2011

Year	MCM Product	Institution	Threat Area	NIH Grant Identifier
2011	AverTox (Galantamine HBr)	CounterVail Corp.	Neurological	U01 NS059344
2013	Versed (Midazolam)	Meridian, a subsidiary of Pfizer, Inc.	Neurological	U01 NS056975
2015	Alteplase (tPA)	University of Colorado, Denver	Pulmonary (Sulfur Mustard)	U54 ES015678
2016	R-107	Radikal Therapeutics, Inc.	Pulmonary (Chlorine)	U01 ES021154
2017	TRPV4 Channel Blocker	GlaxoSmithKline	Pulmonary (Chlorine)	U01 ES015674

Table 6: 2011–2017 NIH-Funded Projects of Chemicals Affecting the Nervous System

Project Identifier	Project Title	Principal Investigator(s)	Institution
U54 NS058183	Center for Catalytic Bioscavenger Medical Defense Research II: Discovery, Formulation, and Preclinical Evaluation	Cerasoli, D.M.	USAMRICD
U54 NS079202	Novel Anticonvulsant and Neuroprotective Therapies for TETS and OP Intoxication	Lein, P.J.	University of California, Davis
U01 NS056975	Neurologic Emergencies Treatment Trials Network: Clinical Coordinating Center	Barsan, W.G.	University of Michigan
U01 NS058162	Efficacy of GluR5 Antagonists Against Soman-Induced Seizures and Neuropathology	Braga, M.F.	Henry M. Jackson Foundation for the Advancement of Military Medicine
U01 NS058213	Parathion Exposure: Mechanisms of Toxicity and Treatment	Delorenzo, R.J.	Virginia Commonwealth University
U01 NS058158	Prostanoid Modulators That Reduce Brain Injury After Seizures	Dingledine, R.J.	Emory University
U01 NS057994	Induced Therapeutic Overexpression of AChE *In Vivo*	Rotundo, R.L.	University of Miami School of Medicine
U01 NS074926	Rational Polytherapy in the Treatment of Cholinergic Seizures	Wasterlain, C.G.	Brentwood Biomedical Research Institute
U01 NS083452	Pharmacotherapy To Counteract Parathion-Induced NMJ Dysfunction	Bird, S.B.	University of Massachusetts Medical School Worcester
U01 NS083448	Improved Standard of Care Reactivators and Facilitative Transport into the Central Nervous System	McDonough, J.H.	USAMRICD
U01 NS083457	Intralipid: A Novel Frontline Countermeasure for Brodifacoum Poisoning	Feinstein, D.L.	University of Illinois, Chicago
U01 NS079249	Developing Drugs To Mitigate Parathion Intoxication	Laskin, J.D.	RBHS-School of Public Health
U01 NS083422	Neuroprotective Effects of AEOL 10150 Against OP Toxicity	Patel, M.N.	University of Colorado, Denver
U01 NS083460	Neurosteroid Treatment for OP Intoxication	Reddy, D.S.	Texas A&M University Health Science Center
U01 NS083430	Brain-Penetrating AChE Reactivators for Several OPs	Chambers, J.E.	Mississippi State University
U01 NS087983	Reactivation of Aged AChE: Design and Development of Novel Therapies	Hadad, C.M.	Ohio State University

Project Identifier	Project Title	Principal Investigator(s)	Institution
U01 NS083451	Accelerated AChE Reactivator Design by Mechanistic Neutron Scattering Studies	Radic, Z.	University of California, San Diego
U01 NS092495	Molecular Imaging of Chemical Threats and Countermeasures	Thompson, C.M.	University of Montana
U01 NS102131	Neurosteroids as a Standard MCM for OP Poisoning	Gee, K.W.	University of California, Irvine
U01 NS105058	Novel Counteract Agents To Reduce Mortality and Morbidity Following OP SE	DeLorenzo, R.J.	Virginia Commonwealth University
R21 NS072079	*In Vivo* Pharmacokinetic and Pharmacodynamic Dispositions of Positron Radiolabeled Ligands	Thompson, C.M.	University of Montana
R21 NS072097	Development of Drugs To Mitigate Parathion Intoxication	Laskin, J.D.	University of Medicine and Dentistry of New Jersey Robert Wood Johnson Medical School
R21 NS072084	High Affinity Capturing Agents for Strychnine	Lam, K.S.	University of California, Davis
R21 NS072094	Identification of Novel Therapeutic Approaches for TETS and OP Intoxication	Lein, P.J.	University of California, Davis
R21 NS072085	Counteracting Acute and Persistent Effects of OP Intoxication by Endocannabinoids	Pope, C.N.	Oklahoma State University, Stillwater
R21 NS072086	Optimization of Nonpyridinium Oximes for BChE Hydrolysis of OPs in Plasma	Taylor, P.W.	University of California, San Diego
R21 NS076429	Developmental Neurotoxicity of Sarin and Soman in Guinea Pigs	Albuquerque, E.X.	University of Maryland, Baltimore
R21 NS070306	Novel Neuromuscular Protection to Counteract Organophosphorus (OP) Poisoning	Bird, S.B.	University of Massachusetts Medical School Worcester
R21 NS072061	Hypothermia Protects Against OP Toxicity	DeLorenzo, R.J.	Virginia Commonwealth University
R21 ES019762	Perinatal Methylmercury Targets Hippocampal Stem Cells and Reduces Neurogenesis	DiCicco-Bloom, E.M.	RBHS-Robert Wood Johnson Medical School
R21 NS076430	Synthesis of Methylating Ligands That Reactivate Aged AChE	Quinn, D.M.	University of Iowa
R21 NS076426	A Neurosteroid-Based Novel Treatment for OP Intoxication	Reddy, D.S.	Texas A&M University Health Science Center

Project Identifier	Project Title	Principal Investigator(s)	Institution
R21 NS072099	Evaluation of Neuroprotective Effects of AEOL 10150 Against Chemical Threat Agents	Patel, M.N.	University of Colorado, Denver
R21 NS080790	Development of Amodiaquine and Its Analogs as Reactivators of OP-Inhibited AChE	Landry, D.W.	Columbia University Health Sciences
R21 NS076448	Intranasal Central Nervous System Delivery of Drugs Against OP Threat Agents	Namboodiri, A.M.	Henry M. Jackson Foundation for the Advancement of Military Medicine
R21 NS084899	Formulation and Encapsulation of Enzymic Countermeasures Against OP Nerve Agents	Magliery, T.J.	Ohio State University
R21 NS084904	BChE Reactivators for Nerve Agent and Pesticide OP Detoxification in Human Tissue	Radic, Z.	University of California, San Diego
R21 NS084897	Screening Therapies To Counteract Developmental Chlorpyrifos Intoxication	Goldstone, J.V.	Woods Hole Oceanographic Institution
R21 NS084900	Developing and Evaluating Countermeasures Against Tetramethylenedisulfotetramine	Shakarjian, M.P.	New York Medical College
R21 NS094131	Targeting the Glutamatergic System To Counteract Soman Toxicity in Immature Rats	Braga, M.F.	Henry M. Jackson Foundation for the Advancement of Military Medicine
R21 NS089488	Amelioration of Soman-Induced Neuropathology With NAAG-Related Compounds	Mccabe, J.T.	Henry M. Jackson Foundation for the Advancement of Military Medicine
R21 NS103820	The Carboxylesterase Knockout Mouse as a Model To Evaluate the Efficacy of Delayed MCMs Against Soman Exposure	Lange, L.	Geneva Foundation
R21 NS099007	Toxin-Specific and Symptomatic Drugs in Combination With Novel Neuroprotectants Effectively Counteract DFP-Induced Long-Term Neurotoxicity	Thippeswamy, T.	Iowa State University
R21 NS099009	Epigenetic Attenuation of Long-Term Effects of Nerve Agents	Reddy, D.S.	Texas A&M University Health Science Center
R21 NS103831	Computationally Designed Stable Artificial Phosphotriesterases for Detoxification of OP Agents	Montclare, J.K.	New York University

Project Identifier	Project Title	Principal Investigator(s)	Institution
R44 NS068049	Definitive Studies for Use of Galantamine As a Pre-Treatment Countermeasure Against Nerve Agents	Basinger, B.	Countervail Corporation
IAA	2012 Rat and Guinea Pig Models of Nerve Agent Intoxication to Evaluate Delayed Treatment With Novel Anticonvulsants	McDonough, J.H.	USAMRICD
IAA	Neurotransmitter Effects of Nerve Agent and MCM in Freely Moving Animals—An Animal Model for Evaluating Neuroprotectant Drugs	Shih, T.S.	USAMRICD
IAA	Developing a Transgenic GFP-Labeled Neutrophil Zebrafish Model for Real-Time Assessment of Brain Injury Progression and Neuroprotectants Following OP Poisoning	Kan, R.K.	USAMRICD
IAA	Central Nervous System Active Oximes as Delayed Treatments for Nerve Agent Casualties	Koplovitz, I.	USAMRICD
IAA	Mechanistic Characterization of Glutamatergic Excitotoxicity for the Development of a Therapeutic Screening Platform Using ES Cell-Derived Neurons	Hubbard, K.	USAMRICD
IAA	Pediatric Susceptibility to Nerve Agent-Induced Seizures and Effectiveness of Anticonvulsant Treatments	McDonough, J.H.	USAMRICD
IAA	Development of an Aging Rat Model of Nerve Agent Exposure and Evaluation of Standard MCMs in the Aging Model	Moffet, M.	USAMRICD
IAA	Do Nerve Agent-Induced Seizures Alter Synaptic Plasticity in Brain Regions Critical for Memory and Behavior?	McNutt, P.	USAMRICD
IAA	The Development of a Neuroprotective Treatment for Nerve Agent Poisoning Using Central A1 Adenosine Receptor Agonists	Shih, T.S.	USAMRICD
IAA	Evaluation of Anticholinergic and Antiglutamatergic Ligands for Efficacy Against Percutaneous Exposure to VX In Rats	Lange, L.	USAMRICD

Project Identifier	Project Title	Principal Investigator(s)	Institution
IAA	Evaluation of Novel Anticonvulsants to Treat Nerve Agent- and Pesticide-Induced Seizures and Prevent Brain Damage in Pediatric Rats	Miller, S.	USAMRICD
IAA	The Evaluation of the Efficacy of MCMs To Attenuate the Neuropathological and Behavioral Consequences of Soman Exposure in the Aging Rat Model	Moffett, M.	USAMRICD
IAA	Zebrafish: An *In Vivo* High-Throughput Model for Evaluating the Efficacy of Oximes To Reactivate OP-Inhibited AChE	Kan, R.K.	USAMRICD
IAA	2014 Rat and Guinea Pig Models of Nerve Agent Intoxication To Evaluate Delayed Treatment With Novel Anticonvulsants	McDonough, J.H.	USAMRICD
IAA	Evaluation of Cannabinoids as Adjunct to Standard Therapy for Soman-Induced Toxicity in Rats	Sanjakdar, S.	USAMRICD
IAA	Therapeutic Evaluation of Clinically Approved Antiepileptic Drugs To Treat Spontaneous Recurrent Seizures Following Nerve Agent Exposure	Beske, P.	USAMRICD
IAA	Evaluation of Cannabinoids as Adjunct to Standard Therapy for Soman-Induced Toxicity in Rats	Lange, L.	USAMRICD
IAA	Evaluation of Long-Term Inflammatory Consequences Following Cessation of Nerve Agent-Induced Seizures	Skovira, J.	USAMRICD
IAA	The Development of Adenosine Receptor Agonists as Anti-Seizure and Anti-Inflammatory Treatments for Nerve Agent Poisoning Using Pharmacologic, Computational, and Optogenetic Methods	Shih, T.S.	USAMRICD
IAA	Evaluation of Novel Anticonvulsants to Treat Nerve Agent- and Pesticide-Induced Seizures and Prevent Brain Damage in Pediatric Rats	McDonough, J.H.	USAMRICD
IAA	Rat Models of OP and Nerve Agent Intoxication To Evaluate Delayed Treatment With Novel Anticonvulsants/Neuroprotectants	McDonough, J.H.	USAMRICD

Table 7: 2011–2017 NIH-Funded Projects of Chemicals Affecting the Respiratory Tract

Project Identifier	Project Title	Principal Investigator(s)	Institution
U54 ES015678	Novel Antioxidant Therapeutics for Sulfur Mustard Toxicity	White, C.W.	National Jewish Health
U54 ES027698	Development of Antidotes for Toxic Gases	White, C.W.	University of Colorado, Denver
U01 ES015673	Novel Therapies for Chlorine-Induced Lung Injury	Hoyle, G.W.	University of Louisville
U01 ES015674	Targeting Injury Pathways To Counteract Pulmonary Agent and Vesicant Toxicity	Jordt, S.E.	Duke University
U01 ES015675	Functional Genomics of Chemical-Induced Acute Lung Injury	Leikauf, G.D.	University of Pittsburgh
U01 ES021154	Multifunctional Therapeutics for Treatment of Acute Chlorine Inhalational Injury	Southan, G.J.	Radikal Therapeutics, Inc.
U01 ES017219	Development of Therapeutics for Chlorine-Induced Airway and Lung Injury	Gunn, M.D.	Duke University
U01 ES022564	Countermeasures for Chlorine-Induced Airway Fibrosis	Hoyle, G.W.	University of Louisville
U01 ES023759	Nitrite-Dependent Protection Against Cl_2 Gas Toxicity Role of Chlorinated Lipids	Patel, R.	University of Alabama, Birmingham
U01 ES025069	Extracellular RNA as Therapeutic Target After Toxic Chemical Inhalation	Ahmad, A.	University of Alabama, Birmingham
U01 ES024097	Thioredoxin Mimicry: Novel Treatment of Toxicant-Mediated Inhalational Lung Injuries	Southan, G.J.	Radikal Therapeutics, Inc.
U01 ES026458	Bromine Inhalation-Induced Lung Injury: Novel Mechanisms and Treatment Strategies	Matalon, S.	University of Alabama, Birmingham
U01 ES027697	Cialis Reverses Halogen-Induced Injury to Pregnant Animals and Their Offspring	Matalon, S.	University of Alabama, Birmingham
U01 ES028187	TIE2 Activation for the Treatment of Chemical-Induced Acute Lung Injury	Kontos, C.D.	Duke University
U01 ES028182	Targeting Cardiopulmonary Calpains To Mitigate Toxicity of Halogen Gases	Ahmad, S.	University of Alabama, Birmingham
U01 ES015675	Functional Genomics of Chemical-Induced Acute Lung Injury	Leikauf, G.D.	University of Pittsburgh
R21 ES020123	Repair of Airway Epithelium Following Chlorine Lung Injury	Hoyle, G.W.	University of Louisville
R21 ES020124	Countermeasure for Chlorine Inhalation	Suman, S.G.	SRI International

Project Identifier	Project Title	Principal Investigator(s)	Institution
R21 ES022875	Accelerating Inflammation Resolution To Counteract Chemical Injury	Jordt, S.E.	Duke University
R21 ES022876	Finding Effective Treatments for Inhaled Chlorine-Induced Injury-Related Pain	Ness, T.J.	University of Alabama, Birmingham
R21 ES024030	Novel Treatments of Acrolein-Induced Cardiotoxicity	Conklin, D.J.	University of Louisville
R21 ES024029	TIE2 Activation for the Treatment of Chemical-Induced Acute Lung Injury	Kontos, C.D.	Duke University
R21 ES024027	Mitochondrial Bioenergetic Dysfunction and Chlorine Toxicity	Matalon, S.	University of Alabama, Birmingham
R21 ES024028	Intracellular Targeting Hsp70 for Pulmonary Cytoprotection After Toxin Inhalation	Parseghian, M.	Rubicon Biotechnology, Inc.
R21 ES026830	Atropine for Chlorine Inhalation Toxicity	Veress, L.A.	University of Colorado, Denver
R21 ES027391	Treatment of Persistent Chlorine-Induced Small Airway Disease	Hoyle, G.W.	University of Louisville
R21 ES027390	Countermeasure Therapeutics for Acute Lung Injury	Leikauf, G.D.	University of Pittsburgh
R21 ES029309	Antidotes Against Hydrochloric Acid-Induced Chronic Lung Injury	Catravas, J.D.	Old Dominion University
R21 ES029310	An Approach Toward Antidotes for Phosphine	Pearce, L.L.	University of Pittsburgh
IAA	2012 Continuing Studies on Treatments for Phosgene-Induced Lung Injury	Anderson, D.	USAMRICD
IAA	2012 Phosphine Poisoning: Model Development, Toxicity, Mechanisms, and Treatment	Sciuto, A.M.	USAMRICD
IAA	2014 Continuing Studies on Treatments for Phosgene-Induced Lung Injury	Anderson, D.	USAMRICD
IAA	2014 Phosphine Poisoning: Model Development, Toxicity, Mechanisms, and Treatment	Sciuto, A.M.	USAMRICD
IAA	Assessment of Treatment Strategies Following Inhalational Ammonia Exposure	Perkins, M.	USAMRICD
IAA	2016 Phosphine Poisoning: Model Development, Toxicity, Mechanisms, and Treatment	Wong, B.	USAMRICD
IAA	2016 Treatments for Phosgene-Induced Lung Injury	Anderson, D.	USAMRICD

Table 8: 2011–2017 NIH-Funded Projects of Chemicals Affecting the Skin, Eyes, and Mucous Membranes

Project Identifier	Project Title	Principal Investigator(s)	Institution
U54 AR055073	Rutgers University CounterACT Research Center of Excellence	Laskin, J.D.	Rutgers Biomedical and Health Sciences School of Public Health
U01 AR064144	Amelioration of Vesicant-Induced Skin Injury by High Dose 25-Hydroxyvitamin D	Lu, K.Q.	Case Western Reserve University
U01 EY023143	Effective Therapies for Ocular Injuries by Vesicating Agents	Agarwal, R.	University of Colorado Denver
U01 NS095678	Blocking Arsenicals-Induced Cutaneous Injury	Athar, M.	University of Alabama, Birmingham
U01 AR071168	Translation of Novel and Repurposed Drugs To Address the Acute and Late Effects of Mustard Exposure	Lu, K.Q.	Case Western Reserve University
R21 AR064595	Therapeutic Intervention of Lewisite-Mediated Cutaneous Blistering-Inflammation	Athar, M.	University of Alabama, Birmingham
R21 EY026777	Therapy for Ocular Mustard Gas Exposure Using Engineered FGF Derivatives	Eveleth, D.D.	E and B Technologies, LLC
R21 EY026776	Glutathione Monoesters To Counteract Ocular Chemical Injury	Vasiliou, V.	Yale University
R21 AR073544	Phosgene Oxime Cutaneous Toxicity and Mechanisms To Identify Therapeutic Targets	Tewari-Singh, N.	University of Colorado Denver
IAA	High Throughput *In Vitro* Mechanistic siRNA Screening for Identification and Validation of Therapeutic Targets for Toxic Industrial Chemical Ocular Injury	Ruff, A.	USAMRICD
IAA	Posttranscriptional Target Regulation by MicroRNAs and RNA Binding Proteins During Cutaneous Vesicant Damage	Yego, E.C.	USAMRICD
IAA	2014 Vesicant and Toxic Industrial Chemical Ocular Injury: High-Throughput Screening Approaches To Identify Therapeutic Targets and Understand Mechanisms of Injury	Ruff, A.	USAMRICD
IAA	Evaluation of Rho Kinase (ROCK) Inhibitors To Improve Corneal Recovery From Ocular SM Exposure and Prevent Long-Term Corneal Pathologies	McNutt, P.	USAMRICD

Project Identifier	Project Title	Principal Investigator(s)	Institution
IAA	Evidence-Based Selection and Pre-Clinical Evaluation of First-Line Limbotrophic Therapies for Post-Exposure Treatment of Ocular Sulfur Mustard Injuries	McNutt, P.	USAMRICD
IAA	2016 Vesicant and Toxic Industrial Chemical Ocular Injury: High-Throughput Screening Approaches To Identify Therapeutic Targets and Understand Mechanisms of Injury	Ruff, A.	USAMRICD
IAA	Generation of a Bioengineered Posterior Cornea Construct for Use in Evaluating Mechanisms of Ocular Vesicant Injury	Varney, T.	USAMRICD

Table 9: 2011–2017 NIH-Funded Projects of Chemicals Affecting Cellular Respiration

Project Identifier	Project Title	Principal Investigator(s)	Institution
U54 NS079201	A Discovery and Development Pipeline for Cyanide Countermeasures	MaCrae, C.A.	Brigham and Women's Hospital
U01 NS058030	Pre-Clinical and Clinical Studies of Cobinamide, a New Cyanide Detoxifying Agent	Boss, G.R.	University of California, San Diego
U01 NS058087	Countermeasures Against Chemical Threats: Countermeasures Against Cyanide	Patterson, S.E.	University of Minnesota
U01 NS087964	Development of the Vitamin B12 Analog Cobinamide as a Hydrogen Sulfide Antidote	Boss, G.R.	University of California, San Diego
U01 NS097162	Methylene Blue as an Antidote Against Hydrogen Sulfide Intoxication	Haouzi, P.	Pennsylvania State University Hershey Medical Center
U01 NS105057	Sodium Tetrathionate as a Cyanide Antidote	Boss, G.R.	University of California, San Diego
R21 NS072105	Testing the Vitamin B12 Analog Cobinamide Against Selected Chemical Threats	Boss, G.R.	University of California, San Diego
R21 NS080799	Protection of Brain Injury From Cyanide Poisoning by Carnosic Acid	Lipton, S.A.	Sanford Burnham Prebys Medical Discovery Institute
R21 NS080788	Crystalline Hydroxocobalamin and Methemoglobin as a Treatment of H2S Intoxication	Haouzi, P.	Pennsylvania State University Hershey Medical Center

Project Identifier	Project Title	Principal Investigator(s)	Institution
R21 NS084894	Nitrites as Antidotes for Hydrogen Sulfide Poisoning	Peterson, J.	University of Pittsburgh
R21 NS090017	Methylene Blue, a Novel Treatment of H2s Poisoning-Induced Brain Injury	Haouzi, P.	Pennsylvania State University Hershey Medical Center
R21 NS089893	Cyanide Decorporation by Co(Iii) Schiff-Base Macrocycles	Pearce, L.L.	University of Pittsburgh
R21 NS089487	Efficacy of Cobinamide for Treatment of Hydrogen Sulfide-Induced Neurotoxicity	Rumbeiha, W.K.	Iowa State University
R21 NS098991	Effects of Acute Administration of the Phenothiazinium Chromophore Methylene Blue During Life-Threatening Cyanide Intoxication	Haouzi, P.	Pennsylvania State University Hershey Medical Center
R21 NS098989	New Chelating (Decorporating) Agents for Azide	Pearce, L.L.	University of Pittsburgh
R21 NS103826	Mitochondrial Targeted Biofuels as Countermeasures Against Chemical Threats	Kilbaugh, T.J.	Children's Hospital of Philadelphia
R43 NS076359	Development of a Field-Deployable Device To Rapidly Measure Blood Cyanide Levels	Boehringer, H.	Diagnostic Consulting Network, Inc.
R44 NS076359	Development of a Field-Deployable Device To Rapidly Measure Blood Cyanide Levels	Boehringer, H.	Diagnostic Consulting Network, Inc.
IAA	Collaborative Studies for Acceleration of Advanced Cyanide Antidote Agents for Mass Casualty Exposure Treatment	Rockwood, G.	USAMRICD
IAA	Cyanide Antidotes for Mass Casualties: Comparison of Intramuscular Injection by Autoinjector, Intraosseous Injection, and Inhalation Delivery	Rockwood, G.	USAMRICD
IAA	*In Vivo* Efficacy and Optimization of Novel Cyanide Countermeasures	Rockwood, G.	USAMRICD
IAA	Assessment of Gene Expression Patterns in Cardiac and Brain Tissues After Cyanide Exposure To Identify Novel Drug Targets for Drug Therapy	Gangwer, K.	USAMRICD
IAA	Establishing a Realistic Model of Ingested Chemical Agents	Myers, T.	USAMRICD

Project Identifier	Project Title	Principal Investigator(s)	Institution
IAA	Preclinical Development of Novel Cyanide MCMs	Downey, J.	USAMRICD
IAA	Efficacy Testing of Next-Generation Cyanide Antidotes	Allen, A.	USAMRICD
IAA	Characterization of Single and Combinatorial Drug Therapies Against Acute Oral Tetramine Poisoning	Myers, T.	USAMRICD
IAA	Investigating Therapeutics for Toxicological Effects of Sodium Fluoroacetate Metabolic Poisoning	McCranor, B.	USAMRICD
IAA	Preclinical Development of Novel Cyanide MCMs	Aragon, M.	USAMRICD
IAA	Assessment of Gene Expression Patterns in Cardiac and Brain Tissues After Exposure to Cyanide in the Absence and Presence of Candidate Cyanide Countermeasures	DeLeon, S.	USAMRICD

Figure 1: PHEMCE Agencies and Partnerships and Their Roles in Advancing National Preparedness for Natural, Accidental, and Intentional Threats

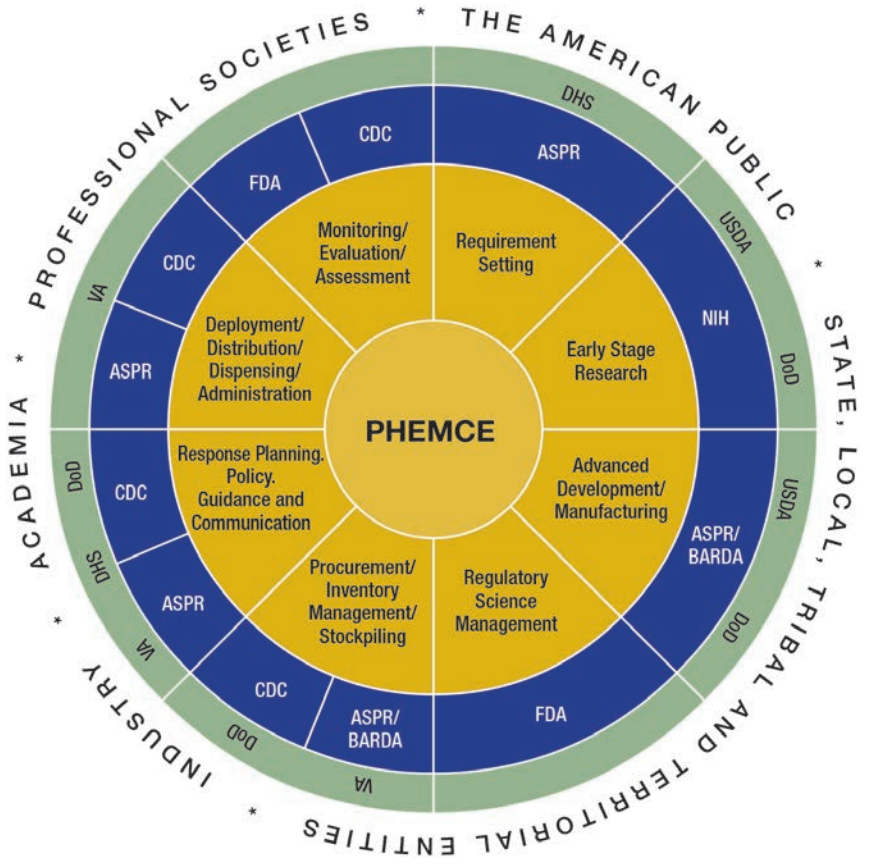
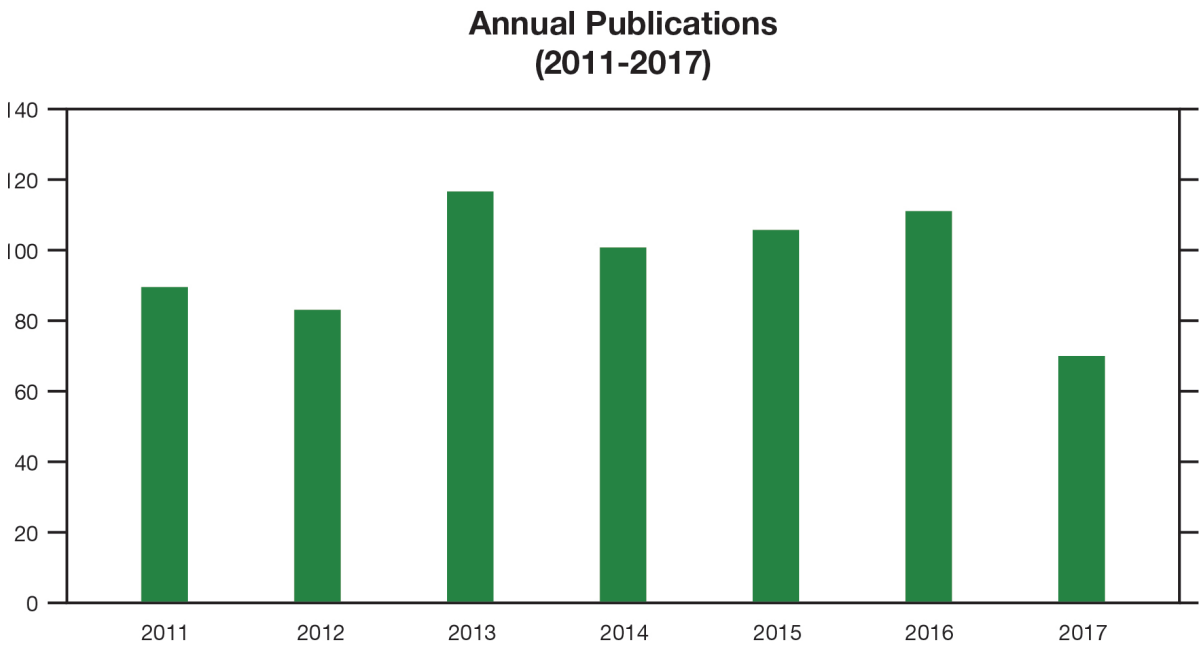


Figure 2: Annual Publications Resulting From CCRP Investments Since the Last Progress Update in 2011 as Reported by the QVR Bibliography Report (678 Total)



Appendix A: Examples of Highly Hazardous Chemicals That Have Been Studied by the CCRP

Chemicals Affecting the Nervous System	
Cholinergic Chemical Warfare Agents (CWAs)	Tabun (GA) Sarin (GB) Soman (GD) Cyclosarin (GF) VX
Cholinergic Pesticides	Aldicarb Chlorpyrifos Diisopropylfluorophosphate (DFP) Disulfoton Methomyl Parathion Phorate
Convulsant Agents	Tetramine (TETS) Picrotoxin Strychnine
Chemicals Affecting the Respiratory Tract	
Pulmonary Agents and Irritants	Acrolein Ammonia Bromine Chlorine Chloropicrin Hydrochloric Acid Phosgene Phosphine Sulfur Mustard
Chemicals Affecting the Skin, Eyes, and Mucous Membranes	
Vesicating Agents	Diphenylcyanoarsine (DA) Diphenylcyanoarsine (DC) Ethyl Dichloroarsine (ED) Lewisite Phosgene Oxime Nitrogen Mustard Sulfur Mustard

Chemicals Affecting the Cellular Respiration	
Blood and Metabolic Agents	Hydrogen Cyanide Hydrogen Sulfide Methyl Isocyanate Methyl Mercaptan Potassium Cyanide Sodium Azide Sodium Fluoroacetate

Appendix B: Key Personnel From Participating ICs

Jill R. Harper, Ph.D.
National Institute of Allergy and Infectious Diseases
Director, Office of Biodefense Research and Surety

Gennady E. Platoff Jr., Ph.D.
National Institute of Allergy and Infectious Diseases
Director, Chemical Countermeasures Research Program

David T. Yeung, Ph.D.
National Institute of Allergy and Infectious Diseases
Deputy Director, Chemical Countermeasures Research Program

Houmam H. Araj, Ph.D.
National Eye Institute

Kristopher J. Bough, Ph.D.
National Institute on Drug Abuse

Pertti (Bert) J. Hakkinen, Ph.D.
National Library of Medicine

David A. Jett, Ph.D.
National Institute of Neurological Disorders and Stroke

Elizabeth A. Maull, Ph.D.
National Institute of Environmental Health Sciences National Toxicology Program

Srikanth S. Nadadur, Ph.D.
National Institute of Environmental Health Sciences

Shardell M. Spriggs, Ph.D.
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Robert F. Tamburro Jr., M.D.
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Hung Tseng, Ph.D.
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National Institute of
Allergy and
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