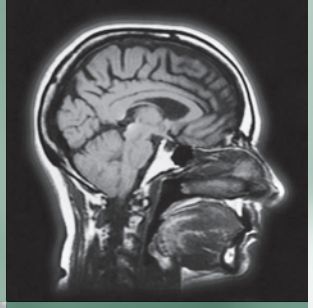
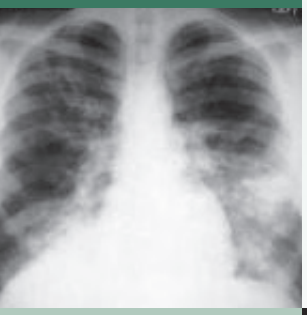
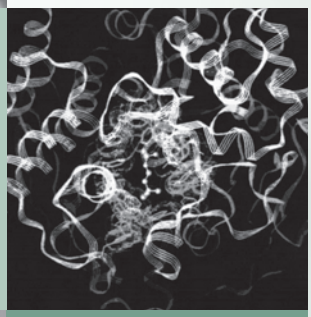


NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Chemical Threats





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

NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Chemical Threats

Coordinated by the Office of Biodefense Research
NIAID

August 2007

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

National Institute of Allergy and Infectious Diseases

FOREWORD

In 2003, the United States Department of Health and Human Services (DHHS) asked the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) to ascertain the availability of medical products that could be used in a chemical terrorist attack in the United States, and to develop a comprehensive research plan for the development of new medical countermeasures that would be useful during and following such an event. For many years, the Department of Defense (DoD) has invested in a research program to develop medical and non-medical chemical defenses for U.S. military forces. The DoD research efforts addressed the classical chemical warfare threats such as sarin, soman, VX, and mustard gas, as well as novel chemical threats to military forces operating throughout the world. With the increasing threat of terrorism, the development of medical products for use in the event of a chemical attack on civilians has become a high priority, but civilian-focused research is beyond the mission of the DoD. Such research more appropriately resides within DHHS which, until recently, has not had a program to develop and stockpile medical products for chemical threats.

This *NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Chemical Threats* is the culmination of NIH planning efforts to develop medical countermeasures against chemical threats to civilian populations with NIAID serving as the main coordination and implementation Institute. This Plan and Research Agenda complements the research strategies already developed by NIAID against biological, radiological, and nuclear threats. It also takes into account the ongoing efforts of other federal agencies and departments, and is consistent with current threat assessment of chemical attacks on civilian populations.

The success of the program outlined in this plan will depend on cooperative efforts and partnerships with other federal agencies, academia, and industry, and the integration of cutting-edge research with the latest technological advances in science and medicine. Research institutes across NIH, particularly the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Environmental Health Sciences (NIEHS), contributed to the development of this Plan and Research Agenda and will be directly involved in its implementation. Other NIH Institutes will also be engaged, as appropriate. This research program was initiated through a special congressional supplement to the NIH budget beginning in fiscal year 2006, with the full support of DHHS.

Elias A. Zerhouni, M.D.
Director
National Institutes of Health

Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases and Chairman, NIH Biodefense Research Coordinating Committee

Table of Contents

FOREWORD i

INTRODUCTION 1
- Previous Research on Medical Countermeasures Against Chemical Threats 1

RESEARCH STRATEGY 3
- General Principles 3
- Overall Short-Term Goals 3
- Overall Long-Term Goals 4

RESEARCH AGENDA 5

I. Chemicals Affecting the Nervous System 5
- Current Medical Countermeasures 5
  - Pretreatment 5
  - Post-Exposure Treatment 5
  - Diagnosis 6
- Potential Medical Countermeasures 6
- Short-Term Goals 7
- Long-Term Goals 8

II. Chemicals Affecting the Respiratory Tract 8
- Current Medical Countermeasures 9
  - Pretreatment and Post-Exposure Treatment 9
  - Diagnosis 9
- Potential Medical Countermeasures 9
- Short-Term Goals 10
- Long-Term Goals 10

III. Chemicals Affecting the Skin, Eyes, and Mucous Membranes 11
- Current Medical Countermeasures 11
  - Pretreatment 11
  - Post-Exposure Treatment 11
  - Diagnosis 11
- Potential Medical Countermeasures 11
- Short-Term Goals 12
- Long-Term Goals 12

IV. Chemicals Affecting Cellular Respiration 12
- Current MedicalCountermeasures 13
  - Pretreatment and Post-Exposure Treatment 13
  - Diagnosis 13
- Potential Medical Countermeasures 13
- Short-Term Goals 14
- Long-Term Goals 14

Appendix 1. Panelists for the NIH Expert Blue Ribbon Panel on Medical Chemical Countermeasures 15

Appendix 2. Participants for the NIH Expert Blue Ribbon Panel on Medical Chemical Countermeasures 17

Appendix 3: Other Key Participants Involved in the Development of the "NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Chemical Threats" 21

Table 1. Names & Symbols of Classical Chemical Warfare Agents with Time of Onset for Initial and Delayed Symptoms 24

INTRODUCTION

The events of September and October 2001 exposed the vulnerability of the United States to acts of terrorism that employ unconventional weapons and tactics. Chemical warfare agents and highly toxic industrial chemicals could also be employed in an attack on a civilian population. Chemicals have long attracted the attention of terrorists, because such toxic materials represent simple weapons that could have devastating effects on the general public. Indeed, in 1995, the Japanese terrorist cult Aum Shinrikyo produced the nerve gas sarin that they used in an attack in the Tokyo subway. Twelve civilians were killed and over 5,000 sickened. In addition, recent events in Iraq in which insurgents used chlorine gas demonstrate the attractiveness of chemicals as weapons of mass destruction.

Several threat scenarios involving chemicals include the deliberate release of illegally obtained or manufactured chemical warfare agents, the release of purchased or stolen industrial chemicals, and attacks on chemical manufacturing plants, storage sites, or transport vehicles. Moreover, the potential also exists for the malicious use of chemicals to contaminate food or water sources.

Several industrial accidents that caused many casualties highlight the potential impact of a terrorist attack on chemical storage sites or transport vehicles. In 1984, a methyl isocyanate leak at a Union Carbide plant in Bhopal, India, killed as many as 5,000 people and injured more than 14,000. In the United States since 2002, three major chlorine gas leaks—one due to a ruptured hose, another due to the rupture of a tanker in a train accident, and the third due to an industrial fire—caused several deaths. Explosions in a chemical plant could also disseminate toxic materials into the atmosphere and surrounding grounds, thus causing an environmental health emergency.

The number and variety of different chemicals that pose a health risk to civilian populations is daunting. Terrorists could use any of the traditional chemical warfare agents, ranging from nerve gas and cyanide to pulmonary and vesicating (blister-causing) agents (see Table 1). A variety of toxic industrial chemicals could be released in a terrorist attack or by accident, and these chemicals could also undergo dangerous reactions following release. The Occupational Safety and Health Administration (OSHA) has identified almost 100 toxic industrial chemicals (TICs), and the Environmental Protection Agency (EPA) lists over 600 chemicals in its Toxic Release Inventory. Animal, plant, and bacterial toxins that can be synthesized are also potential chemical threats.

Previous Research on Medical Countermeasures Against Chemical Threats

The U.S. Army Medical Research Institute of Chemical Defense (USAMRICD) has a long history of developing medical countermeasures against chemical warfare agents. However, because of significant differences between members of the military and civilians, these countermeasures may need to be adapted or expanded for use in a civilian population. One key difference is the demographics of the at-risk population. The typical soldier is a healthy young to middle-aged adult, whereas the civilian population includes a wider spectrum from the very young to the elderly. Many civilians have pre-existing health problems, possibly increasing their risk of injury during a chemical incident. These groups may require modified treatment courses, such as reduced dosages of standard therapies.

A chemical terrorist attack or accident that affects a civilian population may involve a larger range of dangerous compounds than an attack on members of the military. As a result, the effort to develop countermeasures for civilians must place a high priority on rapid screening tests and encompass treatments for exposure to a broader range of dangerous chemicals. Ideally,

medical interventions should be effective against more than one agent, but this may not always be possible. Also, therapeutic compounds may require different formulations depending on how they are to be used. For example, inhalation therapies that are inappropriate for war fighters wearing protective equipment may, nevertheless, be desirable for treating civilians.

NIH has traditionally funded research on some of the symptoms associated with chemical exposures. This research included studies on seizures, memory deficits, and pulmonary edema due to other causes. NIH also has supported research on environmental toxicology. However, no research program has focused on the threat to civilians posed by intentionally released toxic chemicals. The NIH Expert Blue Ribbon Panel on Medical Chemical Countermeasures and several targeted workshops on specific issues related to chemical terrorism assisted NIH in the development of the medical research strategy and agenda described in this document. (Panelists and participants are listed in Appendices 1–3). This research, on the development of medical countermeasures against chemical agents that could be used to cause mass casualties in civilian populations, represents a new and important priority for NIH and DHHS and their commitment to protect and maintain the health of the nation.

RESEARCH STRATEGY

General Principles

This document presents an NIH strategic research plan and research agenda to improve the nation's ability to diagnose, prevent, and treat injuries resulting from chemical attacks or accidents. The guiding principles are:

- Treatments must be appropriate for a diverse civilian population
- Treatment strategies must take into account how a toxic chemical enters the body and the time window for possible medical intervention (see Table 1)
- Treatments must be formulated so they can be administered easily and rapidly in a situation involving mass casualties
- Rapid diagnostic tests must be reliable and easily used in mass casualty situations
- Immediate as well as long-term effects of exposure to chemicals must be understood
- Drugs should be chemically and physically stable so that they are amenable to pre-positioning and stockpiling
- Pretreatments for first responders are desirable especially when decontamination is not possible

Overall Short-Term Goals

NIH has identified important short-term goals based on current knowledge of chemical threats and existing medical products. The following goals include evaluating promising drugs and interventions, and expanding research to accelerate product development:

- Identify medical products approved by the Food and Drug Administration (FDA) that could be used to treat or prevent chemically induced injuries in civilian populations
- Conduct appropriate studies to document the efficacy and safety of promising medical products for use as chemical countermeasures in order to obtain FDA approval
- Develop the capacity to conduct preclinical studies with Good Laboratory Practices (GLP) and Good Manufacturing Practices (GMP) in order to meet FDA approval requirements for an Investigational New Drug (IND) application
- Expand the current NIH research infrastructure to support clinical trials on promising medical chemical countermeasures
- Encourage pharmaceutical and biotechnology industries to engage in the development of medical products pertinent to the NIH research agenda
- Identify and validate appropriate in vitro and animal models for preclinical drug testing
- Establish a research network with focused projects to conduct basic, translational, and clinical research
- Develop and support collaborative research facilities that will foster inter-governmental, industrial, and academic partnerships, in full compliance with applicable chemical safety and security regulations

Overall Long-Term Goals

NIH has also identified the following important long-term goals based on gaps in fundamental scientific knowledge and specific needs for medical countermeasures that are currently non-existent or at early stages of development:

- Determine how chemical agents are absorbed, distributed, metabolized, and eliminated by the human body as a means of identifying targets for intervention
- Identify the mechanisms of action of specific chemical agents and their sites of injury, from the systemic to the molecular level
- Identify effective routes of administration for promising drugs
- Identify common physiological responses to chemical exposure, such as oxidative stress and immune reactions
- Investigate the healing mechanisms following chemical injury and identify novel ways to accelerate recovery processes
- Develop and validate new screening models for the rapid identification of promising therapeutic and prophylactic drug candidates
- Develop rapid screening and assessment tools to improve the triage process during mass casualty events, and to differentiate levels of exposure
- Develop medical prophylactic measures appropriate for use by first responders or other individuals who must operate in a chemically contaminated environment
- Identify biological markers that indicate exposure to specific chemical agents and the level of exposure
- Determine the long-term health effects resulting from exposure to specific toxic chemicals, and establish databases for clinical, epidemiological, and laboratory information that will contribute to this understanding

RESEARCH AGENDA

I. Chemicals Affecting the Nervous System

A variety of chemicals are known to affect the nervous system. Some directly target neural signaling pathways. These include the classic nerve agents (e.g., sarin, soman, tabun, and VX), organophosphate pesticides, and some animal toxins (e.g., botulinum toxin). Chemicals can also affect the nervous system indirectly. For example, metabolic poisons (e.g., cyanide) disrupt cellular respiration, which ultimately prevents the brain from getting sufficient oxygen and energy. Some vesicating agents (e.g., sulfur mustard) appear to have neurological effects as well, although the specific mechanism by which they affect the nervous system is poorly understood.

Neurological symptoms depend on the type of chemical, the level of exposure, and the time elapsed following exposure. Exposure to nerve agents, metabolic poisons, or high levels of sulfur mustard can trigger seizures and loss of consciousness. Other acute effects of nerve agent poisoning include muscle paralysis, cardiorespiratory depression, massive secretion from mucous membranes, eye irritation, and blurry or dim vision. Other acute effects of exposure to high doses of sulfur mustard include behavioral effects and cognitive difficulties. Nerve agents and metabolic poisons also appear to have serious long-term neurological effects, including neurodegeneration, but these have not been studied extensively.

The physical states of chemicals that affect the nervous system are an important determinant of the requirements for developing effective countermeasures. Although some chemicals that affect the nervous system exist primarily in the form of a vapor (e.g. hydrogen cyanide), others are oily liquids that are very difficult to remove from the environment and extremely toxic even at miniscule levels (e.g., VX). For these persistent agents, it would be ideal to have pretreatments with long-lasting protective effects that can be administered in advance of possible exposure to personnel who must enter contaminated sites.

Current Medical Countermeasures

Existing medical countermeasures target the molecular interactions between nerve agents and proteins involved in neural signaling. Neurons can communicate with each other or stimulate muscle cells by releasing a chemical called acetylcholine. Nerve agents and organophosphate pesticides bind and inhibit a protein called acetylcholinesterase (AChE), which normally breaks down acetylcholine after a stimulated neuron has released it. The acute symptoms of nerve agent and organophosphate exposure are due to excess acetylcholine that persists after its release and continues to stimulate nerve endings in the brain, muscles, and secretory glands. Although this route of nerve excitation is considered to be the major focus for drug intervention, other neurotransmission pathways in the body that can be affected by toxic chemicals may need to be assessed separately for the development of potential interventions.

Pretreatment

The U.S. military adopted pyridostigmine bromide (PB), an FDA-approved treatment for myasthenia gravis (an autoimmune disease characterized by extreme muscle weakness), for the pretreatment of soman (a nerve gas) poisoning. PB competes with the nerve agent by reversibly attaching to AChE prior to nerve agent exposure, thus avoiding the toxic effects of excessive acetylcholine stimulation. PB has limited usefulness after exposure to a nerve agent and is approved for use in military populations against only one of several nerve agents that could be used in an attack.

Post-Exposure Treatment

The standard treatment for nerve agent and organophosphate poisoning includes a

combination of atropine sulfate, the oxime 2-PAM, and benzodiazepine anticonvulsants, such as diazepam. Atropine blocks acetylcholine receptors in certain tissues, drying secretions and reducing smooth muscle contraction. Oximes free AChE from the chemical nerve agent and have their most marked effect on skeletal muscle strength. The only oxime approved for use in the United States against nerve agents is pralidoxime chloride (2-PAM). This oxime is also indicated as an antidote for organophosphate insecticide poisoning and to control overdosage of anticholinesterase drugs in the treatment of myasthenia gravis. The Strategic National Stockpile CHEMPACKs, which have been distributed around the United States for deployment in case of a chemical attack or accident, contain military "Mark I" adult autoinjectors with atropine and 2-PAM, diazepam autoinjectors, pediatric atropine autoinjectors, and multi-use vials of 2-PAM and diazepam.

These current treatments for nerve agent or organophosphate exposure have significant disadvantages. Multiple doses of atropine and 2-PAM may be necessary in order to be effective. Atropine does not relieve nerve agent effects on skeletal muscles. Oximes are ineffective once the AChE-nerve agent complex has undergone "aging," a chemical change that permanently inactivates AChE. Aging can happen within minutes of exposure to some of the nerve agents, such as soman. Although diazepam is an effective treatment for nerve agent-induced seizures during about the first 40 minutes after exposure, it is less useful later. Benzodiazepine anticonvulsants also carry risks of excessive sedation and respiratory depression. No treatments are currently available to prevent or reduce neurodegeneration resulting from prolonged seizures, anoxia, or the direct effects of chemical agents.

Diagnosis

Diagnosis following an acute exposure to a nerve agent is generally based on clinical observations of specific symptoms. Environmental sensors may provide valuable information on probable chemical exposure. One of the greatest challenges in diagnosis is determining whether an individual exposed to a nerve agent is experiencing chemically induced seizure activity in the absence of visible convulsions, since the chemicals that trigger seizures may also cause unconsciousness or paralysis. Sustained seizure activity that is uncontrolled can result in permanent brain injury and death. The standard test for seizure activity involves placing electrodes on the scalp to record electrical activity in the brain using electroencephalography (EEG). Such devices are not portable and have limited practical value in evaluating patients in a mass casualty situation.

Potential Medical Countermeasures

Alternative oximes, such as trimedoxime (TMB4), Toxogonin, and HI-6 (an H-series oxime), are available in other countries for the treatment of nerve agent-induced injuries. Some of these have been or are in the process of being evaluated for use by the U.S. military, but none have been evaluated for possible use in U.S. civilian populations. Several promising new oxime candidates also have been identified and will require further investigation.

Proteins such as the enzyme butyrlcholinesterase (BChE), which have a similar structure to AChE, represent another potential therapeutic approach. They can act as "bioscavengers," sequestering nerve agent molecules in the bloodstream. Plasma-derived human BChE shows some promise as a prophylactic countermeasure for military personnel, but it remains uncertain whether this product can be administered efficiently in a large enough volume to be fully effective. Several studies are underway and more are needed to determine if this, and similar bioscavenger-like proteins, could be effective treatments for civilians after exposure to a nerve agent has already occurred. Alternative forms of BChE have been produced through genetic engineering. They appear to be effective as pretreatments in animal models, and it may be possible to develop these

enzymes as treatments for the civilian population or pretreatments for first responders.

Several promising anticonvulsant drugs for the treatment of nerve agent poisoning are on the horizon. New anticonvulsant drugs that have been or are being developed for the treatment of epilepsy in pediatric and adult populations may also be useful for treating chemically induced injuries. Alternative or more expeditious delivery routes for anticonvulsant drugs already approved to treat seizures may also be desirable in the event of mass casualties.

The benzodiazepine midazolam, currently FDA-approved as an intravenous sedative and anesthetic, may also be very effective in the treatment of seizures. Midazolam is being investigated to replace diazepam as the immediate anticonvulsant treatment for nerve agent-induced seizures. The potential use of midazolam, administered intramuscularly, to treat nerve agent-induced seizures will require clinical trials to test its effectiveness and gain FDA approval. Different benzodiazepines and other classes of drugs that antagonize various neuronal excitation pathways mediated by the neurotransmitter glutamate and neurosteroids, are also candidates to treat chemically induced seizures. The development of these potential therapies will also require preclinical and clinical studies.

Other promising research strategies may lead to treatments for chemically induced, long-term damage to the nervous system, or neurodegeneration. Recent studies have shown that the immunosuppressant drug cyclosporine dramatically reduced organophosphate-induced seizures and brain damage, and preserved memory and learning ability in rodents. Clinical trials are planned or underway with several drugs that appear to slow or stop the process of neurodegeneration due to stroke, traumatic brain injury, and chronic nervous system diseases. Some of these drugs may be candidates to prevent chemically induced neurodegeneration.

Short-Term Goals

- Initiate appropriate clinical studies to determine the safety and efficacy of promising anticonvulsants, such as midazolam, that would lead to FDA licensure, and explore the use of such products in different populations
- Establish a drug development program that includes preclinical drug screening and clinical studies on potential anticonvulsant and neuroprotective therapies
- Identify and validate appropriate models for preclinical drug testing, including in vitro systems and animal models, to investigate the effects of high and low levels of exposure to nerve agents
- Expand knowledge of how different nerve agents are absorbed, distributed, metabolized, and eliminated by the body, and explore the interactions of agents with current antidotes
- Determine optimal drug formulations of the most promising medical countermeasures, and safe and effective route(s) of administration
- Explore the practical use of enzyme bioscavengers that could be used to treat victims after exposure to nerve agents
- Establish a collaborative research effort with DoD to develop medical countermeasures against nerve agents of greatest concern, capitalizing on current and future DoD research
- Develop a comprehensive medical research program that involves academia and industry in the development of specific medical countermeasures directed against nerve agents

Long-Term Goals

- Expand knowledge of the mechanisms by which chemical agents affect the nervous system and its neuroexcitatory pathways
- Expand knowledge of the physiological responses to toxic chemicals, including oxidative stress, at the cellular and molecular levels, and the inflammatory changes and other immune responses following chemical exposure
- Identify mechanisms and types of injury and recovery associated with specific nerve agents and the anti-seizure responses to anticonvulsants
- Identify any differences in the susceptibility of different civilian populations to the toxic effects of nerve agents
- Determine the applicability and safety of specific medical countermeasures to different subpopulations in the United States, to include those with pre-existing illnesses or taking other medications
- Identify acute and chronic neurological effects of exposure to high and low levels of chemical agents and strategies for intervention
- Identify new rapid screening techniques or diagnostic tools that can be used in the evaluation of individuals during and following suspected chemical exposure
- Identify biomarkers of injury to help identify the specific chemicals responsible for observed neurological symptoms
- Support technologies used in portable assessment devices that could prove useful in the initial evaluation and treatment of chemically induced seizures during a mass casualty situation
- Evaluate different safe and effective routes of administration of FDA-approved anticonvulsants and other drugs
- Develop new enzyme reactivators that are broadly effective against groups of nerve agents, including those agents, such as soman, that make the body refractory to treatment over time
- Develop bioscavengers that can break down nerve agents into inert substances
- Evaluate approaches to eliminate and/or deactivate nerve agents from body surfaces and open wounds to prevent further absorption, exposure, and injury
- Develop appropriate animal models of acute and chronic chemically induced neurological injury that parallel the human experience
- Establish databases of clinical, epidemiological, and laboratory information that will contribute to the understanding of the mechanisms of nerve agent-induced injury, and the acute and chronic effects of high and low level exposure

II. Chemicals Affecting the Respiratory Tract

Many toxic chemicals can damage the respiratory airways, with potentially life-threatening effects. Ammonia, various alkalis (e.g., bleach and sodium hydroxide), hydrochloric and sulfuric acid, vesicants (e.g., sulfur mustard) and other corrosive agents affect the upper airways, the portion of the respiratory tract that begins at the mouth and nose and ends at the larynx (voice box). Inhalation of these chemicals can cause acute inflammation, painful ulcerations, increased secretions, and difficulties in breathing and swallowing. Secondary bacterial infections may further exacerbate the initial injury. Damage to

the upper airway can lead to respiratory failure and death. Exposure can also lead to long-term health problems. For example, chronic respiratory problems, such as scarring and narrowing of the trachea, have been observed in Iranians exposed to sulfur mustard during the Iran-Iraq War of the 1980s. (Vesicating chemicals will be discussed in more detail in the section entitled "Chemicals Affecting the Skin, Eyes, and Mucous Membranes.")

Some industrial chemicals, including ammonia, chlorine, phosgene, and perfluoroisobutylene (PFIB) can cause lower respiratory tract injuries, particularly life-threatening pulmonary edema. Pulmonary edema—the leakage of fluid into the lungs—prevents oxygen delivery to the blood, ultimately preventing oxygen from reaching the brain, kidneys, and other organs. Symptoms may be immediate or delayed; chlorine causes immediate airway irritation and pain, whereas phosgene exposure may not be evident for 24 to 48 hours (see Table 1). People who survive a single, acute exposure to respiratory airway toxins generally show little or no long-term health problems, although some may eventually develop asthma or chronic bronchitis. Individuals at greatest risk are those with pre-existing heart or lung disease.

Current Medical Countermeasures

Pretreatment and Post-Exposure Treatment

Specific pretreatments, drugs to prevent chemically induced lung injuries due to respiratory airway toxins, are not available. Analgesic medications, oxygen, humidification, and ventilator support currently constitute standard therapy. Hemorrhaging, signifying substantial damage to the lining of the airways and lungs, can occur with exposure to highly corrosive chemicals and may require additional medical interventions. Treatment of injuries to the lower respiratory tract is also supportive and usually includes administration of oxygen, the use of mechanical ventilation to include positive airway pressure, and bronchodilators to treat bronchospasms. Drugs that reduce the inflammatory response, promote healing of tissues, and prevent the onset of pulmonary edema or secondary inflammation may be used following severe injury to prevent chronic scarring and airway narrowing.

Diagnosis

Current diagnostic capabilities are limited. Exposure to chlorine, phosgene, or any of the major alkalis is determined based on clinical signs and symptoms. No screening tests are available to identify individuals exposed to low levels of chemicals.

Potential Medical Countermeasures

Although current treatments can be administered in a controlled hospital setting, many hospitals are ill-suited for a situation involving mass casualties among civilians. Inexpensive positive-pressure devices that can be used easily in a mass casualty situation, and drugs to prevent inflammation and pulmonary edema are needed. Several drugs that have been approved by the FDA for other indications hold promise for treating chemically induced pulmonary edema. These include β2-agonists, dopamine, insulin, allopurinol, and non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen. Ibuprofen is particularly appealing because it has an established safety record and can be easily administered as an initial intervention. Studies have shown that ibuprofen improves survival and reduces lung fluid levels in mice exposed to phosgene. Inhaled and systemic forms of β2-agonists used in the treatment of asthma and other commonly used medications, such as insulin, dopamine, and allopurinol have also been effective in reducing pulmonary edema in animal models but require further study.

Other promising drugs in earlier stages of development act at various steps in the complex molecular pathways underlying pulmonary edema. Some of these potential drugs target the

inflammatory response or the specific site(s) of injury. Others modulate the activity of ion channels that control fluid transport across lung membranes or target surfactant, a substance that lines the air sacs in the lungs and prevents them from collapsing. Mechanistic information based on toxicology, biochemistry, and physiology may be instrumental in determining new targets for therapy.

Mechanistic studies may also aid in the development of new diagnostic approaches. Some chemicals generate metabolic byproducts that could be used for diagnosis, but detection of these byproducts may not be possible until many hours after initial exposure. Additional research needs to be directed at developing sensitive and specific tests to identify individuals quickly after they have been exposed to varying levels of chemicals toxic to the respiratory tract.

Short-Term Goals

- Identify and validate appropriate in vitro systems and animal models for preclinical testing of drugs to treat chemically induced injury to the upper and lower respiratory tract
- Identify products approved by the FDA for other indications that have potential for the treatment and/or prevention of chemically induced pulmonary edema
- Conduct appropriate studies to document the safety and efficacy of commonly used anti-inflammatory drugs following acute exposure to chemicals such as chlorine and phosgene
- Assess the effectiveness of current medical interventions for lung injury as they apply to the treatment of chemically induced pulmonary edema
- Develop collaborations among academia, government, nonprofit organizations, clinical research networks, and research centers that are specifically focused on chemical agents that induce pulmonary edema
- Develop a database and registry of individuals exposed to high quantities of toxic chemicals to the respiratory tract

Long-Term Goals

- Determine specific mechanisms and sites of injury to the respiratory tract, from the systemic to the molecular level, for the major chemical threat agents
- Identify the healing processes and immune responses in the respiratory tract following chemically induced injury, and identify windows of opportunity for intervention
- Identify new drugs and therapeutic regimens using appropriate animal models that simulate lung injury in humans
- Identify chronic health effects associated with low and high doses of inhaled toxic chemicals and methods to prevent these effects
- Develop diagnostic tools and biological markers associated with acute lung injury
- Identify new diagnostic methods that are non-invasive and can continuously assess pulmonary function, lung inflammation, and lung injury
- Identify risk factors associated with chronic effects of lung injury, and develop strategies to prevent development of such chronic changes
- Encourage the development of a more portable state-of-the-art, positive-pressure ventilation device that could be used in

patients with acute respiratory distress during mass casualty events

III. Chemicals Affecting the Skin, Eyes, and Mucous Membranes

Vesicating agents such as sulfur mustard, nitrogen mustard, lewisite, and caustic industrial chemicals can cause severe blistering and burns to the eyes, mucous membranes, skin, and upper airways, as well as chronic eye inflammation and blindness. The eyes are the organs most sensitive to these chemicals. Vesicants may also affect other parts of the body, including the respiratory tract, immune system, and bone marrow. Sulfur mustard can cause tissue damage within minutes of exposure. Physical injury from other vesicating agents may not be evident for several hours and may result in delayed recognition of exposure (see Table 1). In such situations, an exposed individual may put others at risk of secondary contamination.

Current Medical Countermeasures

Pretreatment

Sulfur mustard is an oily liquid and is considered a "persistent" chemical agent, i.e., it does not evaporate quickly and remains active for an extended time. Clothing, skin, and hair may remain contaminated with sulfur mustard for hours, presenting a challenge to health care providers. The military and first responders rely heavily on individual physical protection (e.g., protective masks and suits) to prevent exposure to vesicants. No pretreatment drugs are yet available.

Post-Exposure Treatment

Current treatment of vesicant-induced injuries is largely symptomatic and supportive. Eye injuries require the use of special eye drops, antibiotics, and other drugs to prevent secondary infection, and steroids to limit the inflammatory response and speed the healing process. Skin wounds, especially when severe with blister formation, require specific medical attention to reduce pain, prevent infection, and reduce inflammation. Debridement (removal) of a layer of the injured skin may be necessary to speed the healing process.

British-Anti-Lewisite (BAL, also known as dimercaprol) is a specific antidote for the chemical agent lewisite and is also used for the treatment of heavy metal poisoning. BAL skin and eye ointments were developed for the U.S. military and have been shown to decrease the severity of skin and eye lesions when applied quickly after exposure.

Diagnosis

At this time, diagnosis of vesicant injury is based on clinical signs and symptoms and the detection of specific agents in the environment. There are no FDA-approved clinical laboratory tests for sulfur mustard in blood or tissue. However, compounds such as thiodiglycol (TDG) are produced in the body after exposure to sulfur mustard and can be detected in blood, urine, and tissue. Analysis of these compounds requires the use of complex technologies such as gas chromatography-mass spectrometry.

Potential Medical Countermeasures

BAL may be useful in the topical treatment of non-blister injuries from other vesicants in addition to lewisite. Because of reported toxicities associated with BAL, however, this compound has not been considered to be a useful prophylactic drug. Other therapeutic compounds are needed that can prevent or quickly reduce the redness and deep tissue damage (blisters). Also needed are improved skin protectants, reactive skin protectants that can neutralize the agent, new skin and eye therapies, and improved healing techniques.

Short-Term Goals

- Evaluate medical countermeasures used by DoD for the treatment of vesicating injuries for their use in civilian populations during mass casualty situations
- Evaluate and monitor promising ophthalmic drugs developed by DoD and assess their applicability for civilian populations and first responders
- Identify FDA-approved skin protectants against chemical agents for potential use in civilian populations
- Identify and validate appropriate in vitro systems and animal models for preclinical drug testing to develop treatments for injuries from caustic agents and vesicants

Long-Term Goals

- Develop novel therapeutic strategies, including reactive therapeutic compounds, to prevent blister formation and inflammatory effects in skin and eyes
- Evaluate the effectiveness of new immunotherapeutic compounds and their applicability in the treatment of injuries caused by acids, alkalis, or sulfur mustard
- Identify the mechanisms of action of specific chemical agents and their sites of injury to the skin, eyes, and mucous membranes, from the systemic to the molecular level
- Investigate the healing mechanisms following chemical injury, and identify novel ways of accelerating the recovery process
- Identify and utilize information about the mechanisms of action of vesicants on tissues, organs, and the hematopoetic system for the development of therapeutic interventions
- Evaluate novel therapeutic strategies for acid- and alkali-induced injuries
- Identify biological markers consistent with exposure to various types of chemical agents and levels of exposure to such agents
- Evaluate "reactive" or "catalytic" skin protectants for use in civilian populations, such as first responders who must operate in a contaminated environment
- Evaluate decontamination approaches for patients with open-wound injuries, and identify novel opportunities for medical intervention
- Develop practical therapies that can be administered easily and safely to decontaminate the skin during mass casualty situations

IV. Chemicals Affecting Cellular Respiration

Metabolic poisons, such as hydrogen cyanide and cyanogen chloride, inhibit cellular respiration, whereby cells extract oxygen from the blood and transform the energy in sugar molecules into a useful form of energy for cells. All systems of the body are ultimately affected by these metabolic poisons. The cardiovascular and central nervous systems are most strongly affected, due to their high demands for oxygen and energy, and their limited ability to use alternative pathways for energy production. Exposure to metabolic poisons can quickly cause seizures, respiratory failure, cardiac arrest, and death. The long-term effects of these agents are poorly understood and may include gradual neurodegeneration.

Metabolic poisons can be inhaled or ingested. Exposure to high concentrations of hydrogen

cyanide gas (HCN) can cause death within minutes. This narrow therapeutic window presents a formidable challenge for treatment but emphasizes the need for immediate medical intervention. Inhalation of lower concentrations of cyanide vapor or the ingestion of cyanide salt may result in a slower development of symptoms.

Current MedicalCountermeasures

Pretreatment and Post-Exposure Treatment

No pretreatment for cyanide poisoning is available and may not be practical. Since 1933, a Cyanide Antidote Kit has been marketed for use in the United States but, as a kit, it has never received formal regulatory approval by FDA. The Cyanide Antidote Kit includes crushable ampules of amyl nitrite, for inhalation, and sodium nitrite and sodium thiosulfate, which are administered intravenously. The nitrites bind with hemoglobin in the blood to produce methemoglobin molecules. The methemoglobin then binds with cyanide to produce a much less toxic compound, cyanomethemoglobin, which is eventually eliminated from the body. Sodium thiosulfate, often referred to as a sulfur donor drug, converts cyanide into non-toxic thiocyanate, which is then excreted by the kidneys.

Use of the Cyanide Antidote Kit can be very effective as a post-exposure treatment for cyanide poisoning, but it carries the risk of toxic side effects. High levels of methemoglobin can be lethal. Determining the correct dose is especially challenging for treating pediatric casualties. Individuals with pre-existing glucose 6-phosphate deficiency (G6PD deficiency, the most common inherited enzyme deficiency in humans) have a risk of red cell hemolysis if given sodium thiosulfate. Individuals with renal deficiency or anemia could also suffer toxicity from the treatment. Concern has been raised over the ability to quantify predictably the amount of amyl nitrite that would be absorbed through inhalation.

Recently the FDA approved Cyanokit (hydroxocobalamin for injection) for the treatment of cyanide poisoning. It has not yet been determined how effective this new countermeasure would be in a mass casualty situation.

Administration of 10 percent (hyperbaric) oxygen is a major component in the treatment of cyanide poisoning and is typically used even before the administration of any cyanide antidotes. However, the value of hyperbaric oxygen has not been determined, especially with products that form methemoglobin.

Diagnosis

Because ingredients in cyanide antidote kits can have toxic side effects, accurate diagnosis of cyanide poisoning is important. Currently, diagnosis is based on clinical evaluation, but the presenting symptoms may be confused with exposure to other agents including nerve agents, botulinum toxin, hydrogen sulfide, or carbon monoxide. No rapid diagnostic tests are available for any cyanide-containing compounds.

Potential Medical Countermeasures

Cobinamide, one of the compounds in the biosynthesis pathway of hydroxocobalamin, is another promising drug that warrants further investigation. Cyanohydrin-forming compounds (e.g., alpha-ketoglutarate and pyruvate) and vasodilatory drugs that act similarly to nitrite compounds are potential new cyanide antidotes, as are drugs that act at the cellular level, such as synthetic S-substituted crystallized rhodanese (an enzyme that promotes the conversion of cyanide to non-toxic thiocyanate). Sulfur-containing medications may also have potential benefits in the treatment of cyanide poisoning, especially those that remain in circulation for longer periods of time than sodium thiosulfate. Drugs that form methemoglobin may have an advantage, but there are significant health risks associated with high levels of methemoglobin.

Several sophisticated cyanide detection methodologies have been developed but these are neither rapid nor widely available.

Short-Term Goals

- Improve understanding of the mechanisms of injury, from the systemic to the cellular level, from cyanide-containing compounds, and identify potential targets for medical intervention
- Identify FDA-approved drugs containing sulfur that may have therapeutic value in the treatment of cyanide poisoning
- Determine optimal and novel routes of administration of promising drug compounds, to include administration through inhalation
- Identify screening tests and biological markers consistent with the identification of hydrogen cyanide and/or cyanide metabolite(s) and the level of exposure to such agents
- Identify and validate appropriate in vitro systems and animal models for preclinical testing of drugs that could be useful for the treatment of cyanide poisoning
- Validate the use of oxygen therapy in the initial treatment of cyanide poisoning, alone or in combination with other medical countermeasures
- Understand the differences in cyanide intoxication between civilians of different ages, and establish a treatment plan for susceptible populations

Long-Term Goals

- Conduct safety and efficacy studies with promising drugs and identify effective routes of administration that would lead to timely intervention
- Identify the major mechanisms and pathways by which sulfur donors, methemoglobin formers, and cobalt compounds counteract cyanide toxicity in different systems of the body
- Expand the NIH research infrastructure to enable preclinical and clinical studies of compounds with promising anti-cyanide activity
- Develop rapid diagnostic tests and assays to identify specific biological markers consistent with cyanide exposure and the level of exposure to such agents
- Identify any long-term or chronic health effects resulting from exposure to hydrogen cyanide, the cyanide-containing salts, and/or cyanogen chloride
- Establish databases of clinical, epidemiological, and laboratory information that will contribute to the understanding of the acute and chronic health effects of high- and low-level exposures to cyanide-containing compounds
- Review current therapeutic interventions with oxygen and assess the value of other proposed alternatives, such as the use of hyperbaric oxygen in the treatment of cyanide-induced toxicity

Appendix 1. Panelists for the NIH Expert Blue Ribbon Panel on Medical Chemical Countermeasures

Michael A. Matthay, M.D. (Chairperson)
Professor of Medicine and Anesthesia
University of California, San Francisco
San Francisco, CA

M. Bahi Abou-Donia, Ph.D.
Professor of Pharmacology and Cancer Biology
Professor of Neurobiology
Duke University
Durham, NC

Francine Benes, M.D., Ph.D.
Professor of Psychiatry (Neuroscience)
McLean Hospital
Belmont, MA

Thomas P. Bleck, M.D.
Professor of Neurology, Neurological Surgery and Internal Medicine
Department of Neurology
University of Virginia
Charlottesville, VA

James C. Cloyd, PharmD.
Professor and Lawrence C. Weaver
Endowed Chair–Orphan Drug Development
McGuire Translational Research Facility
College of Pharmacy
University of Minnesota
Minneapolis, MN

Clem Furlong, Ph.D.
Research Professor of Medicine
University of Washington
Seattle, WA

Joe N. Garcia, M.D.
Lowell T. Coggeshall Professor of Medicine
Chairman, Department of Medicine
University of Chicago Hospitals
Chicago, IL

Thomas A. Gasiewicz, Ph.D.
Professor and Chair
Department of Environmental Medicine
University of Rochester
Rochester, NY

Rogene F. Henderson, Ph.D., DABT
Scientist Emeritus
Lovelace Respiratory Research Institute
Albuquerque, NM

Gary Isom, Ph.D.
Professor of Toxicology and Molecular Pharmacology
Department of Medicinal Chemistry
School of Pharmacy and Pharmacology
Purdue University
West Lafayette, IN

Stephen M. Milner, M.D.
Chief, Division of Burns
Surgical Director, Johns Hopkins Wound Healing Center
Johns Hopkins Burn Center
Johns Hopkins Bayview Medical Center
Baltimore, MD

William C. Mobley, M.D., Ph.D.
Professor and Chair, Department of Neurology and Neurological Sciences
Stanford University
Stanford, CA

Dean S. Rosenthal, Ph.D.
Associate Professor of Biochemistry and Molecular Biology
Georgetown University School of Medicine
Washington, DC

Palmer Taylor, Ph.D.
Professor of Pharmacology
Dean, Skaggs School of Pharmacy and Pharmaceutical Sciences
University of California, San Diego
Department of Pharmacology
La Jolla, CA

James L. Way, Ph.D.
Professor of Pharmacology and Toxicology (retired)
Texas A&M University
San Francisco, CA

Roberta F. White, Ph.D.
Professor and Chair
Department of Environmental Health
Boston University School of Public Health
Boston, MA

Appendix 2. Participants for the NIH Expert Blue Ribbon Panel on Medical Chemical Countermeasures

DEPARTMENT OF HEALTH AND HUMAN SERVICES (DHHS)

Office of Public Health Emergency Preparedness (OPHEP)

Jerome Donlon, M.D., Ph.D.
Chief Scientist
OPHEP/ DHHS
Washington, DC

Eric Wassermann, M.D.
Senior Medical Advisor
Medical Chemical Countermeasures
OPHEP/DHHS
Washington, DC

NATIONAL INSTITUTES OF HEALTH (NIH)

National Institute of Allergy and Infectious Diseases (NIAID),

Anthony S. Fauci, M.D.
Director
NIAID/NIH
Bethesda, MD

Ernest T. Takafuji, M.D., M.P.H.
Director, Office of Biodefense Research
NIAID/NIH
Bethesda, MD

Carole Hudgings, Ph.D.
Senior Advisor to the Deputy Director
NIAID/NIH
Bethesda, MD

Gennady E. Platoff, Ph.D.
CBRN Scientific Advisor
Office of Biodefense Research
NIAID/NIH
Bethesda, MD

Richard A. Lambert, J.D.
Intellectual Property and Contracts Consultant
NIAID/NIH
Bethesda, MD

Kenneth Millburne, J.D.
Biodefense Program Officer
Office of Biodefense Research
NIAID/NIH
Bethesda, MD

Ranjan Gupta, Ph.D.
Planning and Evaluation Specialist
Strategic Planning and Evaluation Branch
NIAID/NIH
Bethesda, MD

Christine Shamblin, M.S.
Biodefense Program Specialist
Office of Biodefense Research
NIAID/NIH
Bethesda, MD

National Institute of Environmental Health Sciences (NIEHS), NIH

Dennis Lang, Ph.D.
Deputy Director
Division of Extramural Research and Training
NIEHS/NIH
Research Triangle Park, NC

National Institute of Neurological Disorders and Stroke (NINDS), NIH

Story C. Landis, Ph.D.
Director
NINDS/NIH
Bethesda, MD

Robert W. Baughman, Ph.D.
Associate Director for Technology Development
Neuroscience Center
NINDS/NIH
Bethesda, MD

Audrey S. Penn, M.D.
Office of the Director
NINDS/NIH
Bethesda, MD

David A. Jett, Ph.D.
Program Director
Neuroscience Center
NINDS/NIH
Bethesda, MD

Rebecca Farkas, Ph.D.
Science Policy Analyst
NINDS/NIH
Bethesda, MD

National Eye Institute (NEI), NIH

Michael D. Oberdorfer, Ph.D.
Division of Extramural Research
NEI/NIH
Bethesda, MD

National Heart, Lung, and Blood Institute (NHLBI), NIH

Herbert Reynolds, M.D.
Medical Officer
NHLBI/NIH
Bethesda, MD

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIH

Alan N. Moshell, M.D.
Skin Disease Program Director
NIAMS/NIH
Bethesda, MD

National Institute of General Medical Sciences (NIGMS), NIH

Richard Okita, Ph.D.
Health Science Administrator
NIGMS/NIH
Bethesda, MD

FOOD AND DRUG ADMINISTRATION (FDA), DHHS

Brad Leissa, M.D.
Deputy Director
Division of Counter-Terrorism
Center for Drug Evaluation and Research
FDA
Rockville, MD

Narayan Nair, M.D.
CDR, USPHS
Medical Officer
Division of Counter-Terrorism
FDA/CDER/OCTAP/DCT
Silver Spring, MD

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC), DHHS

Angela M. Weber, M.S.
Industrial Hygienist
National Center for Environmental Health
Office of Terrorism Preparedness and Emergency Response
CDC
Atlanta, GA

Jerry D. Thomas, M.D.
Medical Toxicologist
Senior Medical Officer
National Center for Environmental Health
Division of Laboratory Sciences
Emergency Response and Air Toxicants
CDC
Atlanta, GA

DEPARTMENT OF DEFENSE (DOD)

U.S. Army Medical Research and Materiel Command (USAMRMC)

COL James Romano, Ph.D.
Deputy Commander
USAMRMC
Ft. Detrick, MD

U.S. Army Medical Research Institute of Chemical Defense (USAMRICD), DoD

David H. Moore, Ph.D., D.V.M.
Director, Strategic Research Program Development
USAMRICD
Aberdeen Proving Ground, MD

Brennie Hackley, Ph.D.
Senior Scientist
USAMRICD
Aberdeen Proving Ground, MD

Jack Baggett, Ph.D.
Chief, Program Planning and Support Office
USAMRICD
Aberdeen Proving Ground, MD

David E. Lenz, Ph.D.
Research Chemist/Coordinator
USAMRICD
Aberdeen Proving Ground, MD

Tsung-Ming Shih, Ph.D.
Acting Chief, Pharmacology Division
USAMRICD
Aberdeen Proving Ground, MD

Ernest H. Braue, Jr., Ph.D.
Research Chemist
USAMRICD
Aberdeen Proving Ground, MD

John H. McDonough, Ph.D.
Advanced Anticonvulsant and Neuroprotectant Research Coordinator
USAMRICD
Aberdeen Proving Ground, MD

Alfred M. Sciuto, Ph.D.
Chief, Neurotoxicology Branch Pharmacology Division
USAMRICD
Aberdeen Proving Ground, MD

William J. Smith, Ph.D.
Chief, Cell and Molecular Biology Branch
USAMRICD
Aberdeen Proving Ground, MD

Chemical Biological Medical Systems (CBMS), DoD

LTC Keith Vesely, Ph.D., D.V.M.
Deputy Joint Product Manager
Medical Identification and Treatment Systems, CBMS
Ft. Detrick, MD

Ron Clawson, Ph.D.
Deputy Joint Project Manager, CBMS
Ft. Detrick, MD

George Schieferstein, Ph.D.
Pharmaceutical Manager
CBMS
Ft. Detrick, MD

DoD Joint Program Executive Office

COL Jonathan Newmark, M.D.
Medical Corps, U.S. Army
Assistant Joint Program Executive Officer, Medical Systems
Consultant to the Army Surgeon General
Chemical Casualty Care
Falls Church, VA

Defense Threat Reduction Agency, DoD

Ed Wakayama, Ph.D.
Senior Manager for CBM-Med Rad Defense (contractor)
Interim Senior Manager for Pretreatments
Fort Belvoir, VA

Other Federal Agencies

S. Randolph Long, Ph.D.
Director, Chemical Countermeasures
Science and Technology Directorate
Department of Homeland Security
Washington, DC

Jason Boehm, Ph.D.
Policy Analyst
Office of Science and Technology Policy
Executive Office of the President
Washington, DC

Philip Edelman, M.D.
Branch Chief
National Counterterrorism Center
Washington, DC

Appendix 3: Other Key Participants Involved in the Development of the "NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Chemical Threats"

John D. Baldeschwieler, Ph.D.
Professor of Chemistry
Division of Chemistry and Chemical Engineering
California Institute of Technology
Pasadena, CA

Frederic Baud, M.D.
Professor
Réanimation Médicale et Toxicologique
Hôpital Lariboisière
Université Paris 7
Paris, France

Edward H. Bertram, M.D.
Department of Neurology
University of Virginia
Charlottesville, VA

Augustine M. K. Choi, M.D.
Pulmonary, Allergy and Critical Care
Physicians Faculty
UPMC Department of Medicine
University of Pittsburgh
Pittsburgh, PA

Douglas A. Coulter, Ph.D.
Associate Professor of Pediatrics and Neurology
Division of Neurology
Department of Pediatrics
University of Pennsylvania School of Medicine
Philadelphia, PA

Steven Curry, M.D.
Director
Department of Medical Toxicology
Phoenix, AZ

F. Edward Dudek, Ph.D.
Department of Biomedical Sciences
Colorado State University
Ft. Collins, CO

Steven M. Dudek, M.D.
Assistant Professor of Medicine
Pulmonary and Critical Care Medicine
University of Chicago
Chicago, IL

Alan H. Hall, M.D.
President and Chief Medical Toxicologist
Toxicology Consulting and Medical Translating Services
Elks Mountain, WY

Fred Henretig, M.D.
Director
Clinical Toxicology Section
Division of Emergency Medicine and Poison Control Center
Children's Hospital of Philadelphia
Philadelphia, PA

David A. Hosford, M.D., Ph.D.
Research and Development
GlaxoSmithKline
Research Triangle Park, NC

Frances E. Jensen, M.D.
Associate Professor of Neurology
Department of Neurology
Children's Hospital and Harvard Medical School
Boston, MA

Juliann G. Kiang, Ph.D.
Assistant Chief
Department of Cellular Injury
Walter Reed Army Institute of Research
Silver Spring, MD

Mark Kirk, M.D.
Assistant Professor of Emergency Medicine
Division of Medical Toxicology
Department of Emergency Medicine
University of Virginia
Charlottesville, VA

Urmila P. Kodavanti, Ph.D., DABT, USEPA
Pulmonary Toxicology Branch
Experimental Toxicology Division
National Health and Environmental Effects Research Laboratory
Research Triangle Park, NC

Irwin Koplovitz, Ph.D.
Research Coordinator: Improved Oximes
Basic Assessment Branch
USAMRICD
Aberdeen Proving Ground, MD

Joshua Lederberg, Ph.D.
Professor Emeritus
Rockefeller University
New York, NY

Daniel H. Lowenstein, M.D.
Department of Neurology
University of California, San Francisco
San Francisco, CA

Thomas R. Martin, M.D.
Department of Medicine
Veterans Affairs/Puget Sound Medical Center
Seattle, WA

Sadis Matalon, Ph.D.
Professor
Department of Anesthesiology
University of Alabama at Birmingham
Birmingham, AL

Dennis M. Perrotta, Ph.D.
Chief, Bureau of Epidemiology
Texas Department of Health
Texas Poison Center Network
Austin, TX

James Peterson, Ph.D.
Associate Professor
Department of Environmental and Occupational Health
University of Pittsburgh
Pittsburgh, PA

John E. Repine, M.D.
James J. Waring Professor of Medicine and Pediatrics
Division of Pulmonary Sciences and Critical Care Medicine
University of Colorado Health Science Center
Denver, CO

Ian J. Reynolds, Ph.D.
Department of Pharmacology
University of Pittsburgh
Pittsburgh, PA

Gary Rockwood, Ph.D.
Cyanide Research Coordinator
Drug Assessment Division
USAMRICD
Aberdeen Proving Ground, MD

Brett A. Simon, M.D., Ph.D.
Associate Professor
Vice Chair for Faculty Development
Chief, Division of Adult Anesthesia
Department of Anesthesiology
Johns Hopkins School of Medicine
Baltimore, MD

Roger G. Spragg, M.D.
Professor of Medicine
Chief, Medicine Service, La Jolla VA Medical Center
Vice Chair, Department of Medicine
University of California, San Diego
San Diego, CA

Jacob I. Sznajder, M.D.
Pulmonary and Critical Care Medicine
The Feinberg School of Medicine
Department of Medicine
Northwestern University
Chicago, IL

Daniel L. Traber, Ph.D.
Investigational Intensive Care Unit
University of Texas Medical Branch
Galveston, TX

David M. Treiman, M.D.
Newsome Chair in Epileptology
Vice-chair, Neurology
Director, Epilepsy Center
Barrow Neurological Institute
Research Professor of Bioengineering
Arizona State University
Phoenix, AZ

Jianpu Wang, M.D., Ph.D.
Kosair Children's Hospital Research Institute
University of Louisville
Louisville, KY

Claude G. Wasterlain, M.D.
Professor and Vice-Chair, Department of Neurology
University of California, Los Angeles
Los Angeles, CA

H. Steve White, Ph.D.
Director, Anticonvulsant Drug Development Program
Department of Pharmacology and Toxicology
University of Utah
Salt Lake City, UT

George Whitesides, Ph.D.
Chairman, Department of Chemistry
Harvard University
Cambridge, MA

Judith Zelikoff, Ph.D.
Professor of Environmental Medicine
Department of Environmental Medicine
New York University School of Medicine
Tuxedo, NY

Table 1. Names & Symbols of Classical Chemical Warfare Agents with Time of Onset for Initial and Delayed Symptoms

Type	Common Name	Symbol	Time of Onset of Initial Symptoms	Time of Onset of Delayed Symptoms (skin absorption)
Nerve Agents	Tabun	GA (highly volatile)	Seconds to minutes	Within 2 hours
	Sarin	GB (highly volatile)	Seconds to minutes	Within 2 hours
	Soman	GD (highly volatile)	Seconds to minutes	Within 2 hours
	Cyclosarin	GF (highly volatile)	Seconds to minutes	Within 2 hours
	VX	VX (lower volatility)	Minutes	Within 18 hours
Vesicants or Blister Agents	Sulfur Mustard	H and HD	4–6 hours	2–48 hours
	Sulfur Mustard-T Mixture	HT	4–6 hours	2–48 hours
	Nitrogen Mustard	HN-1	4–6 hours	2–48 hours
	Nitrogen Mustard	HN-2	4–6 hours	2–48 hours
	Nitrogen Mustard	HN-3	4–6 hours	2–48 hours
	Lewisite and other arsenical vesicants	L	Immediate	Immediate
Corrosive Skin Irritant	Phosgene oxime	CX	Immediate contact effects; may cause pulmonary edema if inhaled	Immediate (when used with VX, VX absorption is enhanced)
Pulmonary (Choking Agents)	Phosgene	CG	Immediate irritant effects; pulmonary edema 4–48 hours post exposure	N/A
	Chlorine	Cl	Immediate irritant effects; pulmonary edema in 2–4 hours	N/A
	Diphosgene	DP	Immediate irritant effects; pulmonary edema 4-48 hours post exposure	N/A
Blood Agents (Cellular Poisons)	Hydrogen cyanide (vapor and liquid)	AC	< 1 minute (persistence <1 hr)	N/A
	Cyanogen chloride (vapor)	CK	< 1 minute (non-persistent)	N/A

Table based on information in

1. The Medical NBC Battlebook, U.S. Army Center for Health Promotion and Preventive Medicine, May 2000
2. The Textbook of Military Medicine: Medical Aspects of Chemical and Biological Warfare, Office of the Surgeon General, U.S. Army, 1997
3. Department of Health and Human Services CDC Emergency Preparedness and Response information bulletins, 23 September, 2005 (available from: http://www.bt.cdc.gov/chemical/)

Not included in this table are other chemical agents recognized by the military, such as BZ (incapacitating agent), CN and CS (tear gas products), and DM (adamsite), a vomiting gas.

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