MEDICAL CHEMICAL DEFENSE RESEARCH:

AN EXPERT PANEL REVIEW CONDUCTED BY THE

NATIONAL INSTITUTE OF ALLERGY

AND INFECTIOUS DISEASES

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Office of Biodefense Research Affairs
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
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EXECUTIVE SUMMARY

There are increased concerns regarding the potential of terrorists using biological, chemical or radiological agents against the civilian population. In the past, the Department of Defense has maintained a research and development program which addressed these threats for military forces, including primary responsibility for countermeasures related to chemical warfare threats agents. The National Institutes of Health (NIH) is actively assessing relevant opportunities to exploit medical breakthroughs and focus its efforts on the development of new and effective countermeasures for all subsets of the U.S. population. On behalf of the NIH, the National Institute of Allergy and Infectious Diseases (NIAID) convened a special meeting of experts on March 19, 2003, in Bethesda, Maryland, to review ongoing research efforts in the development of medical countermeasures for chemical threats.

The purpose of the meeting was to (1) provide NIAID with an overview of current medical research in chemical defense; (2) identify gaps in scientific knowledge critical to the development of medical products against chemical threats to protect the civilian population; and (3) explore ways in which NIAID/NIH could assist or support efforts in the area of medical research for chemical defense. The meeting included representatives of academia, the chemical industry, poison control centers, private and governmental research institutions, the Office of Homeland Security (The White House), the Society of Toxicology, the Department of Defense, the Department of Health and Human Services, the Centers for Disease Control and Prevention, the Central Intelligence Agency, the U.S. Department of Agriculture, the National Academy of Sciences, and the Institute of Medicine. The results of this meeting will be used by the NIH Biodefense Research Coordinating Committee, as efforts across NIH are coordinated.

The participants recommended that emphasis be placed on the following areas:

- Increase understanding of mechanisms and types of organ, tissue, cellular, and sub-cellular injury from chemicals;
- Expand information on differential individual susceptibility to chemical injury;
- Develop molecular models and well-defined animal models for chemical injury;
- Expand information on low-level acute and chronic health effects from chemicals;
- Increase the availability of medical antidotes for specific subsets of the population;
- Develop easy-to-administer formulations for intravenous, intramuscular, dermal, and/or aerosol administration of drugs;
- Investigate mechanisms to accelerate development of promising antidotes or new labeling of already licensed products; and
- Standardize clinical diagnostic tests and assays for chemical exposure in medical treatment facilities.

BACKGROUND

Chemical warfare has been a continuing concern of the United States. Highly hazardous chemicals with special physical characteristics were developed as tactical weapons by military forces because of their ability to quickly inflict casualties on adversaries. Chemical warfare agents and industrial chemicals that could be used as weapons have now taken on new importance with the realization that terrorist organizations may have more ready access to weapons or hazardous materials capable of causing mass destruction. The evolution of events over the past several years and the increased risk of a domestic terrorist event that could involve the use of deadly chemicals or physical agents have resulted in active engagement of many departments and agencies involved with national security. It is now clear that the chemical threat extends beyond occupational and industrial risks and the need for national preparedness must include terrorist-instigated scenarios. A part of that effort involves an assessment of currently available countermeasures against specific chemical threats, the availability of therapeutic drugs and diagnostic tools for health care providers and first responders, and the need for new medical products or expanded use of existing products.

In 1999, the Institute of Medicine (Health Science Policy Program) and the National Research Council (Board on Environmental Studies and Toxicology, Commission of Life Sciences) were asked to collect and assess existing research, development, and technology information on detecting chemical and biological agents, and to provide recommendations on future research and development efforts. The span of the review included detectors, personal protective equipment, and response capacity within the United States. Nerve agents, vesicants, and cyanide were viewed as the highest chemical agent risks, followed by pulmonary irritants such as phosgene. The report recommended the stockpiling of nerve agent antidotes and called for continuing research on scavenger molecules to be used in immediate post-exposure or pre-treatment scenarios.

In 2002, the National Research Council's Institute of Medicine Committee on Science and Technology for Combating Terrorism reviewed national vulnerabilities and delineated actions for the nation to take. Recommendations included the increased use of sensors to provide an improved capability to detect chemical agents in public areas, and to provide warning, increased training and improved equipment for first responders to enhance their capabilities to detect and treat chemical agent exposures.

The importance of applying technologies to meet needs was emphasized in areas such as detection, filtration, and/or decontamination of air and water. Specific recommendations were made pertaining to the Defense Applied Research Projects Agency, the Food and Drug Administration, the Environmental Protection Agency, the National Institute of Standards and Technology, the Federal Emergency Management Agency as well as other Federal agencies.

Recommendation 4.22 of the report stated:
"Under the guidance of the NIH, there should be a program to develop improved treatments for injuries that result from exposure to chemical agents."... "This program should have both an applied and a fundamental aspect: It should optimize existing protocols, using the most plausible threats, and it should increase our understanding of the general mechanisms of injury on exposure to toxic chemicals. The program should address treatment for both acute and chronic injury, and it should consider countermeasures and protective measures that embrace the full spectrum of threats. Because of the long time required to develop countermeasures, we should start now on important classes of weapons, even if they are not yet known to be ready for deployment."

On March 19, 2003, the Office of Biodefense Research Affairs, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases convened a highly distinguished group of scientists, researchers, and health care providers with special knowledge in chemical defense and national preparedness. The one-day meeting was held at the Hyatt Regency Hotel, in Bethesda, MD.

The purpose of the meeting was to: (1) provide NIAID with an overview of current medical research in chemical defense; (2) identify gaps in scientific knowledge critical to the development of medical products against chemical threats to protect the civilian population; and (3) explore ways in which NIAID/NIH could assist or support efforts in the area of medical research for chemical defense.

Participating in the meeting were representatives from academia; the chemical industry; Federal agencies and departments including the Department of Defense, Office of Homeland Security (The White House), the Food and Drug Administration, the Centers for Disease Control and Prevention, the Central Intelligence Agency, the U. S. Department of Agriculture, the Institute of Medicine and the National Academy of Sciences. Other NIH institutes and centers with an interest in chemical defense were also invited to attend.

This report identifies and discusses specific knowledge gaps in the areas of chemical injury, nerve agents, vesicants, pulmonary "choking" agents, cyanide, and toxins and provides recommendations for research. There are several other classes of potential chemical threats including incapacitating agents, physiological irritants, mind-altering drugs, drugs or chemicals with immunomodulatory effects, and riot-control agents. These compounds are of lesser concern at this time and they were not discussed at the meeting.

CHEMICAL INJURY

The mechanisms of injury for many chemical agents, including chemical warfare agents, are not well understood. Such gaps in knowledge limit the ability to develop effective countermeasures or treatments. Individuals have varying susceptibility to acute and chronic diseases, and thus it is presumed for chemically induced injuries as well. Differential susceptibility and risk factors have not been examined for chemical warfare agents. Changes at the cellular or genetic level following chemical exposure have yet to be fully characterized, and animal models have not been fully developed to study specific types of chemically-induced injury. Advances in molecular biology, including genomic and proteomic tools, provide researchers with new resources for evaluating host factors and the mechanisms of injury.

The acute toxicity of some chemicals has been better studied than others. However, the long-term health effects of many chemicals following low-level exposure have not been extensively evaluated. It is often difficult to ascertain the significance of "minimal" damage at the cellular or sub-cellular level in animal models. Part of the problem has been defining "low-level" exposures, recognizing that guidelines on exposure are not absolute boundaries. While one may think of a terrorist scenario as a single event that causes high-peak exposure to a chemical agent, this may not be the case. Initial exposure to some chemical agents can result in secondary effects, which may not be immediately expressed. Photosensitization, sensitization to other chemicals, and the increased incidence of certain cancers may occur following an initial exposure to some chemical agents.

A large amount of information has been developed to protect individuals from toxic chemicals in workplace settings. Threshold Limit Values (TLV) based on a Time-Weighted-Average (8-hours per day, 40-hours per week in an occupational setting) and Short-Term Exposure Limits (15 minutes of continuous exposure) have been established for many industrial chemicals. Similarly, Threshold Limit Ceiling Values that should never be exceeded have been determined. However, it is difficult to extrapolate these industrial standards to a terrorist scenario.

Rapid medical diagnostic tests for chemical agents are not readily available. Sophisticated analytical laboratories with high pressure liquid chromatography and mass spectroscopy equipment may have the ability to ascertain the presence of specific chemicals and/or their metabolites, but these assays are only available at an extremely small number of laboratories in the country. Health care providers must have diagnostic tests with high sensitivity and specificity at their disposal in order to render the best care to their patients. Highly sensitive screening tests that are able to identify individuals who have been exposed but are in the early stages of developing serious illness would be useful tools for first responders.

- **Appropriate animal models should be developed and used to define the mechanisms of injury caused by a variety of classes of chemical threats.**

- **Host risk factors that predispose certain individuals to injury from chemical threat agents should be delineated.**
- **The effects of low-level exposure to hazardous chemicals should be evaluated.**
- **Rapid, sensitive and specific screening and diagnostic tests should be developed, especially for those chemical agents for which specific therapeutic interventions are available.**

NERVE AGENTS

Nerve agents are organophosphorus compounds that exert their biological effects through inhibition of the enzyme acetylcholinesterase (AChE). Soman, sarin, tabun and the compounds designated as VX and GF are the five most common military nerve agents. Some insecticides have been developed using less toxic forms of this class of chemicals. These compounds hydrolyze the critical neurotransmitter acetylcholine (ACh) into its two primary components at receptor sites in the neuromuscular junction. When an action potential travels down a nerve to the neuromuscular junction, ACh is released from synaptic vesicles, resulting in a post-synaptic potential that eventually results in a contractile response of a muscle or secretion of a gland. The ACh must then be hydrolyzed by AChE to stop further activity at the receptor site. If AChE is not present, ACh would accumulate and continue to produce bursts of post-synaptic potentials with subsequent continuous responses of target organs, as exhibited by spasms, seizures or hypersecretion. Nerve agent antidotes work by competing with the nerve agent for attachment to AChE thereby blocking its effects with strong or irreversible binding.

One strategy for treatment and possible prevention of the effects of nerve agents is the use of a scavenger molecule. If administered in an acute poisoning scenario with a nerve agent or an organophosphate**,** scavenger molecules bind to the circulating nerve agent thereby rendering it unavailable to attack the AChE at the neuromuscular junction. Butyry1cholinesterase (BuChE), an enzyme normally present in small amounts in the blood and tissues of humans, is an attractive scavenger molecule for the treatment and prevention of nerve agent exposure due to its low toxicity. The U.S. Army Medical Research Institute of Chemical Defense is leading the development of this and other similar products, first for military use but with the potential for civilian application. In studies in animal models, such scavengers were found to protect up to 5LD50 of a test chemical agent without physiological side effects. Another similar enzyme that has been studied with promising results is carboxyesterase.

Oximes are compounds that can speed the reactivation of AChE after they have been bound by nerve agent at cholinergic receptors. Pyridine-2-aldoxime methyl chloride (2-PAM), which has been shown to be very effective in the treatment of organophosphate insecticide poisoning, is the only oxime currently approved by FDA for this use. Over time, a phenomenon known as "aging" occurs when the binding of nerve agent to AChE becomes irreversible; oximes have no effect after aging has occurred. The

nerve agent soman undergoes a rapid aging process and oximes are relatively ineffective against it. Other nerve agents such as VX age more slowly, and oximes are more effective against it. While oximes are useful as nerve agent antidotes, they are not as effective in reversing the biological effects in organs innervated by muscarinic receptors. Therefore, oximes such as 2-PAM have limitations in the treatment of nerve poisoning. Research is underway at the Department of Defense (DoD) to test several promising compounds as replacement for 2-PAM looking for a broader acting nerve agent antidote.

Drugs such as neuroprotectants and antiepileptic medications have been developed and licensed for the treatment of neurological diseases. Because the market for therapeutics to treat injuries caused by chemical threat agents is relatively small, many of these drugs have not been evaluated for this use. For example, DoD researchers have demonstrated that the combination of dantrolene, mannitol and diazepam, all licensed drugs for other indications, may offer improved therapy following nerve agent exposure.

Evaluation of an individual's ability to reason and remember is done via indirect methods, which have not been fully validated. Similarly, it is very difficult to evaluate, in a quantitative manner, changes in personality that could theoretically occur following nerve agent exposure. Additionally, these tests have not been correlated with actual anatomical defects that result from environmental exposure to a nerve agent.

- **The development of promising scavenger molecules effective against a wide variety of chemical nerve agents should be pursued.**
- **The development of oximes that are broader acting than 2-PAM, and have the ability to reverse the permanent binding that can occur with some nerve agents should be pursued.**
- **Critical nerve agent antidotes should be evaluated to determine if they can be safely and effectively administered to infants, children and adults via the intravenous and aerosol routes.**
- **The accelerated development of promising antidotes for chemical nerve agents should be pursued.**
- **Expanded labeling of currently licensed anticonvulsants for use against chemical nerve agents and their utilization in autoinjectors should be pursued.**
- **Objective screening tests that can evaluate behavior and cognitive ability, and can differentiate chemically-induced neurological injury from pre-existing neurological illness need to be developed.**

VESICANTS

A number of vesicants can be used as chemical threat agents including Lewisite, phosgene oxime and mustard. Clinically, Lewisite causes immediate pain on the skin while the effects of mustard are not felt for several hours. Phosgene oxime causes dermal erythema and is of lesser importance.

Vesicants also affect the eyes and lungs. Severe eye damage can occur, especially with liquid mustard delivered via airborne droplets that directly contaminate the eyes. The pulmonary tract can also be affected beginning in the upper passageways with necrosis of the epithelium, and involvement of the lower airways with subsequent deeper inhalation of the agent. The lung parenchyma is usually less affected so the damage is primarily a result of direct contact with the agent. Most deaths from mustard exposure are a result of pulmonary injury complicated by infection (e.g., bronchopneumonia), although pulmonary edema and pleural effusion can occur with high exposures.

Much of the ongoing research within the DoD has centered on the development of countermeasures against mustard. Research has focused on understanding the mechanism of action in tissues, cells and DNA. Anti-inflammatory drugs (e.g., indomethacin), scavenger molecules (e.g., mercaptopyridine compounds), protease inhibitors, and poly (ADP-ribose) polymerase inhibitors (e.g., niacinamide), have been extensively studied for their anti-vesicant actions. Alkylation of DNA is considred to be the beginning of one commonly accepted mechanism of injury. A cascade of metabolic and biochemical events ensues, leading to eventual activation of cellular proteases with separation of the basal epidermal cell layer from the basement membrane in the skin (blister formation). Another mechanism might involve depletion of the free radical scavenger glutathione resulting in a cascade of biochemical events including oxidative stress, lipid peroxidation, and the inactivation of sulfhydryl-containing enzymes, leading to cell death.

- **A better understanding of the mechanisms of action and the pathology of chemical vesicants is needed.**
- **The latest molecular and genomic technologies should be applied to the identification of novel therapeutic strategies for the injuries caused by chemical vesicants.**
- **Already-licensed therapeutics (e.g., anti-inflammatory drugs) and those close to final approval by FDA should be evaluated for use as adjuncts in both the early and late treatment of injury caused by chemical vesicants.**
- **Products to arrest progressive damage, prevent permanent injury and enhance recovery from the effects of chemical vesicants on the eyes and lungs should be pursued.**

PULMONARY "CHOKING" AGENTS

The pulmonary "choking" agents of greatest concern include phosgene (CG), diphosgene (DP), chlorine (02), and chloropicrin (PS). Other chemicals capable of seriously injuring the lungs include ammonia, other oxides of nitrogen, fluorine compounds, sulfur dioxide, hydrochloric acid, fuming nitric acid, arsine, sulfuric acid, and perfluoroisobutylene. Little information is available on how the choking agents cause injury. It is recognized that the permeability of alveolar capillaries increases after exposure, with the resulting accumulation of fluid in alveoli and bronchioles, and pleural effusion. Hypoxia results due to decreased absorptive surface area for exchange of oxygen and carbon dioxide, with an increase in the latter seen in the circulation and in tissues. As a result, pulmonary edema continues to be the most challenging health effect from this class of chemical threat agents.

More information is available on the use of phosgene as a potential chemical threat agent. Phosgene is rapidly hydrolyzed in water resulting in the formation of hydrochloric acid and carbon dioxide. DoD scientists have shown that pulmonary edema caused by phosgene can be ameliorated with drugs such as ibuprofen, eicosatetraynoic acid (ETYA), aminophylline, isoproterenol, intratracheally-administered N-acetylcysteine, dibutyryl cAMP, and certain lung surfactants. Anti-inflammatory drugs such as ibuprofen, indomethacin and methylprednisolone may be somewhat "protective" if used prior to exposure.

- **A better understanding of the mechanisms of injury both during and after exposure to phosgene, including the genetic, molecular and biochemical changes occurring in cells and tissues, is needed.**
- **A non-human primate model for phosgene inhalation mimicking the "real-time" conditions expected in a mass exposure incident is needed.**
- **Licensed drugs that can be used in the prevention or treatment of chemically induced pulmonary edema should be identified.**
- **Drugs that can limit the inflammatory cascade of events produced by phosgene and other choking agents should be developed.**

CYANIDE

Cyanide (CN) is readily available in several forms including gaseous hydrogen cyanide used in fumigation; water-soluble sodium and potassium salts; and copper, mercury, gold and silver salts. Cyanide-containing compounds (cyanogens) used in industrial settings where occupational exposures occur include nitriles used as solvents in the manufacture of plastic, sodium nitroprusside, and numerous synthetic materials that generate hydrogen cyanide when burned.

Cyanide acts by inhibiting mitochondrial cytochrome oxidase resulting in impairment of intracellular oxygen utilization and depression of cellular respiration. The organs with the highest oxygen requirements (brain, heart and liver) are the most severely affected. Cyanide binds with high affinity to sulfur-containing compounds fast and irreversibly. The cyanide anion can also attach in a more reversible manner to metalloenzymes, including the ferric ion in methemoglobin.

The neurological sequelae following exposure to cyanide may occur for up to a year or more. Chronic consumption of cyanide-containing foods is a suspected cause of Parkinson's-like symptoms, encephalopathy, and optic neuropathy. Cyanide has been implicated as a cause of "tobacco amblyopia," a condition seen in chronic smokers. Poorly understood changes in vascular blood flow also occur in acute cyanide poisoning, including an increased cerebral blood flow in dogs. The ingestion of cyanide also leads to much higher levels in the liver than that seen via the inhalation route, a phenomenon that is not well understood.

Cyanide antidote kits are available commercially and each contains two 10-ml ampules of sodium nitrite, two 50-ml vials of sodium thiosulfate; and twelve crushable ampules of amyl nitrite inhalant. Sodium nitrite and amyl nitrite are both methemoglobin formers which provide ferric ion binding sites for the circulating cyanide ions. Sodium thiosulfate, a sulfur donor, combines with the cyanide ion to form sodium thiocyanate which is excreted harmlessly in urine. The formation of methemoglobin by nitrites in an individual who is already compromised may decrease oxygen carrying capacity even further. This situation is often found in victims of smoke inhalation where the use of nitrites is contraindicated. These therapeutic kits are widely distributed to poison control centers across the nation, but they may be in limited supply for a mass-poisoning scenario.

The side effects associated with sodium and amyl nitrite (hypotension, vasodilatation, dizziness and headache) make these drugs less than ideal as adjuncts to be used with sodium thiosulfate. Other drugs, including various cobalt salts and other methemoglobin forming compounds, are being investigated for their usefulness in cyanide poisoning.

Hydroxycobalamin (vitamin B12a) is a relatively safe compound that binds cyanide directly without formation of methemoglobin. Reaction of cyanide with the cobalt ion in hydroxycobalamin forms cyanocobalamin, which is non-toxic**.** The drug, which is used in France to treat cyanide poisoning, has not been approved for this use in the United States. However, the utility of hydroxycobalamin is limited as it must be administered intravenously, large doses are usually needed, and it has a short shelf life.

- **A better understanding of the mechanism of action of cyanide at the molecular level is needed.**
- **The use of antidotes to cyanide poisoning in patients exposed to other toxic hazards such as smoke or industrial chemicals needs further evaluation.**
- **A comparison of the efficacy of hydroxycobalamin alone and in combination with sodium thiosulfate in the treatment of cyanide poisoning should be conducted.**

- **Models should be developed to characterize the long-term effects of acute exposure to cyanide and identify how cyanide-containing compounds are metabolized.**

TOXINS

Toxins are different from chemical warfare agents because of their biological origin and physical characteristics, e.g., they are non-volatile. In reality, many toxins may be more potent than chemical agents, and many can now be produced synthetically. If highly lethal toxins can be synthesized in large quantities, even in crude preparations, and a way found to deliver them to an unprotected, unvaccinated target population, then they could become attractive terrorist weapons. At this time, there is general agreement that botulinum toxin represents the major toxin threat followed by concern over ricin.

Saxitoxin (produced by shellfish) and tetrodotoxin (produced by the puffer fish) are two highly potent marine neurotoxins that block nerve conduction. Their effects simulate those seen with chemical nerve agents. The exact mechanism of action of these toxins is not well understood and prognosis is dependent upon route of administration. Microcystin, a toxin produced by blue-green algae, has a high affinity for the liver and it causes irreversible damage and death. The ease with which some toxins can be synthesized using laboratory equipment and facilities that are easy to obtain has raised the concern for this class of compounds. The development of countermeasures for the toxins will be dependant on a better understanding of their mechanism of action.

- **The development of countermeasures for toxins should be prioritized to first address those with the greatest probability of use by terrorists.**
- **Research on toxins from marine organisms should be enhanced and maintained.**

RESEARCH PRIORITIES FOR MEDICAL CHEMICAL DEFENSE

SHORT-TERM (0-3 YEARS)

- **Research that uses the latest technologies to better understand the mechanisms of injury for a variety of classes of chemical threat agents should be supported.**

- **Anassessment of the current military medical chemical defense products for use in the civilian population should be undertaken.**

- **Countermeasures for chemical threat agents that protect all populations, e.g., the very young, the elderly, immunocompromised and pregnant individuals, should be evaluated and developed.**

- **The expansion of label indications for the use of relevant licensed products following exposure to chemical threat agents should be pursued .**

- **Research to develop standardized diagnostic protocols, assays and reagents to quickly identify chemical agent exposures should be enhanced.**

- **Mechanisms to promote collaboration among governmental organizations and institutions in medical chemical defense research should be encouraged.**

MID-TERM (3-5YEARS)

- **Research to determine the health effects of "low-level" exposure to chemical threat agents, with emphasis on the organ, tissue, genetic, and molecular levels, should be supported.**

- **Understanding of the complex risk factors associated with injury from chemical threat agents should be expanded.**

- **Appropriate animal models useful in the study of the effects of chemical threat agents, including non-human primates, should be developed.**
- **Research to develop countermeasures for chemical agent exposure that can be easily administered by first responders and emergency medical personnel such as aerosol or transdermal delivery, should be supported.**

- **Psychological assessment tools to aid in the understanding of the effects of chemical threat agents on the nervous system should be developed.**

- **Research efforts to address incapacitation agents and mind altering drugs should be prioritized based on intelligence information.**

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