DoD Strategy to Address Low-Level Exposures to Chemical Warfare Agents (CWAs)

MAY 1999

Executive Summary

This report responds to the Strom Thurmond National Defense Authorization Act for Fiscal Year 1999 (H. Rpt. 105-736, Sec 247: Chemical Warfare Defense, Public Law 105-261, 17 October 1998, p. 39 and p. 591), and provides our review of the policies and doctrines of the Department of Defense (DoD) on chemical warfare defense. Based on this review, DoD recommends *no* modifications to policies and doctrine to achieve the objectives set forth in the public law. This report also provides a plan to establish a research program for determining the effects of chronic and low-dose exposures to chemical warfare agents, as requested. This plan is not funded in the Fiscal Year 00 Presidentš Budget nor is it considered for overguidance in the FY01~~0~~5 Program Objective Memorandum (POM).

Following are highlights of the main points and recommendations of the DoD strategy:

- Our review identified an extensive number of doctrinal publications and policies addressing operationally significant concentrations of chemical warfare agents for temporary and short-term exposures.
- Current operational guidance and doctrine focuses on temporary exposures, with some short-term exposure scenarios addressed. Doctrine and policies addressing long-term exposures to low-levels of chemical warfare agents is essentially non-existent for operational scenarios, yet detailed guidance has been developed to address potential exposure scenarios in the occupational or general population setting (*e.g.*, in support of chemical stockpile and chemical demilitarization activities).
- This report provides an initial definition for low-level exposures~~ba~~sed on concentration and duration of exposure~~tha~~t may be revised based on the results of future research. Additionally, research will focus on efforts to validate low-level threats that may cause documented health outcomes among deployed forces.
- Efforts are underway to obtain additional data on potential short-term and long-term operational exposures in support of new policies in this area. Sound, empirically-demonstrated scientific data will be the basis of any required new or revised doctrine, policy, or legislation.
- The Research Plan outlines three tiers of research. *Tier I* would provide data for hazard assessments based on actual low-level exposures, establish methodologies for testing low-level effects, and also will evaluate a limited number of chemical interactions. *Tier II* would validate the methodologies established during Tier I and implement methods to investigate new biomarkers, additional interactions, and potential long-term effects. *Tier III* includes a broad array of activities that may occur in parallel with the other tiers, including program review, quality control, independent peer review, and development of risk assessment and risk management tools.

Contents

> ***"What is there that is not poison? All things are poison and nothing [is] without poison. Solely the dose determines that a thing is not a poison."***
>
> *Paracelsus (1493–1541)*

PURPOSE

This proposed Department of Defense (DoD) strategy is designed to address the objectives laid out in the Strom Thurmond National Defense Authorization Act for Fiscal Year 1999.[1] This Report provides information on efforts and plans to *"review the policies and doctrines of the Department of Defense on chemical warfare defense and modify the policies and doctrine as appropriate to achieve the objectives set forth [in the public law.]"* This Report also outlines the efforts underway within the Department to *"develop and carry out a plan to establish a research program for determining the effects of chronic and low-dose exposures to chemical warfare agents."* This Report is presented in four sections:

Section I provides information on the objectives, scope, and background of the DoD strategy for addressing low-level exposures.
Section II provides an overview of existing policies, doctrine, and guidance relevant to protection, decontamination, detection, and surveillance of exposure to low-levels of chemical warfare agents (CWAs).
Section III provides a listing of ongoing and approved initiatives designed to enhance our scientific understanding of the effects of low-level exposures to CWAs.
Section IV presents the framework for a 5-year Research Plan.

The proposed DoD Strategy and supporting 5-year Research Plan are designed to yield data that will guide the potential evolution of policy and doctrine on exposures to chemical warfare agents. The Strategy describes a general process for determining the needed research as well as a process for initiating projects. It also describes how progress will be reviewed and resulting data integrated into DoD doctrine and policy, if required. The principal objective of the Research Plan is to generate knowledge required for assessments of CWAs and associated battlefield hazards.

[1] Strom Thurmond National Defense Authorization Act for Fiscal Year 1999, Authorization Conference Report, H. Rpt. 105-736, Sec 247: Chemical Warfare Defense (*Public Law 105-261*, 17 October 1998), p.39 and p. 591. Hereafter referred to as P.L. 105-261. The complete text of this language is provided at Annex 2.

SECTION I: Objective, Scope, and Background

I.A. OBJECTIVE. This proposed DoD strategy is designed to address the objectives laid out in P.L. 105-261. Specifically, the objectives of the DoD strategy are (1) to provide information to support, if required, modification of policies and doctrines on chemical warfare defense related to low-level exposures to CWAs, and (2) to develop and carry out a plan to establish a research program for determining the effects of low-level exposures to CWAs. The results of modified policies and doctrine and the research program will ensure that the Department is able to achieve the foremost objectives:

- *to provide for adequate protection of personnel from any low-level exposure to a chemical warfare agent that would endanger the health of exposed personnel*, and
- *to provide solutions for the concerns and mission requirements that are specifically applicable for one or more of the Armed Forces in a protracted conflict when exposures to chemical agents could be complex, dynamic, and occurring over an extended period.*[2]

I.B. BACKGROUND. It is possible that some U.S. forces serving in Iraq during the Gulf War (1990~~9~~1) may have been exposed to low-levels of CWAs. Some have cited this possible exposure as being a possible contributing factor in the unexplained health concerns that have plagued some of the Gulf War veterans.[3] Members of Congress and the General Accounting Office (GAO) have raised concerns regarding the adequacy of the DoD policy, doctrine, and technology to identify, prepare for, and defend troops against the possible adverse effects of exposure to low-level CWA.[4]

In its September 1998 report, the GAO concluded that the "DoD has not developed doctrine that addresses low-level exposures to chemical agents, either in isolation or in combination with other contaminants found on the battlefield." Historically, the DoD Chemical Defense Program has focused primarily on the operational consequences of chemical weapons employment. Development of defensive material has focused on minimizing CWA effects through improvements in contamination avoidance, individual protection, collective protection, decontamination, medical countermeasures, training, and doctrine.

The GAO report identified various ongoing initiatives that attempt to improve aspects of the DoD program, such as initiatives to lower detection limits and response time for CWA detectors. GAO cited the following reasons~~wi~~th which DoD concurs~~for~~ the lack of a doctrine that specifically addresses low-level exposures:[5]

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[2] P.L. 105-261.

[3] For examples, see United States Senate, Committee on Veterans' Affairs, *Report of the Special Investigation Unit on Gulf War Illnesses*, S. Rpt. 105-39, Part I and II, (Washington, D.C.: U.S. Government Printing Office, 1998); or *Presidential Advisory Committee on Gulf War Veterans' Illnesses: Final Report* (Washington, DC: U.S. Government Printing Office, December 1996).

[4] Report to Congressional Requesters: *Chemical Weapons – DoD Does Not Have a Strategy to Address Low-Level Exposures*, United States Government Accounting Office, GAO/NSIAD-98-228, September 1998.

[5] *Ibid*., p. 3.

(1) There is no validated low-level threat,
(2) There is no consensus on the definition or meaning of low-level exposures, and
(3) There is no consensus on the effects of low-level exposures.

Hence, the DoD 5-Year Research Plan and efforts to develop policy and doctrine to address low-level exposures are built on the following unifying principles: (1) *threat validation*, (2) *definition of low-level exposures*, and (3) *effects of low-level exposures*.

I.B.1. <u>Threat Validation.</u> Threat validation is typically a site- or situation-specific determination. While the risks posed by low-level chemical agent residues or other environmental contaminants may be perceived as minimal or non-existent, DoD has accepted that there may be situations where such risks must be incorporated into operational risk management decisions. Several initiatives underway prescribe mechanisms to assess the probability and severity of these types of risks during deployment operations. The proposed strategy includes identification of those initiatives and tools being developed to identify and assess threats. To clarify what is meant by "threat," the following definition is provided:

> ***Threat***. (Also referred to as a ***hazard***) ~~–~~a threat is "any real or potential condition that could cause injury, illness, or death of personnel; damage or loss of equipment or property; or mission degradation (loss of combat power)."[6] In the proposed chemical defense low-level exposure strategy, the focus is on the types of threats that may cause documented health outcomes among deployed personnel.

I.B.2. <u>Definition of Low-Level Exposures.</u> DoD policy and doctrine must be based on a uniformly defined concept of low-level exposures. Currently, there is a lack of consensus on a definition of "low-level" within DoD and throughout the scientific community. In the absence of such a definition, it is appropriate that the DoD establish this and any other definitions of terms that will be addressed by the proposed strategy. The term "low-level" implies both a concentration of a chemical and a type of effect. It is also dependent on an assumed duration of exposure. Therefore, each of the following definitions~~*low*~~*-level exposure concentration* and *duration of exposure*~~are~~ are inherently related and must be understood together:

> ***Low-Level Exposure Concentration:*** For a given chemical, low-level exposure concentrations include exposure for a given duration[*] below which no significant adverse health effects (immediate or delayed) are presumed to occur in accordance with the best available scientific data.
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> [*] While the effects are dependent on the concentration and the duration of exposure, the relationship between concentration and the time (duration) is not linear (*i.e.*, data for a concentration X and a duration Y yielding and effect Z should not be extrapolated linearly.)

Duration of Exposure: The period of time military personnel may be exposed to chemical warfare agents or other hazards cannot be precisely estimated. However, the following dura-

[6] Field Manual 100-14, *Risk Management*, Headquarters Department of the Army, Washington D.C., 23 April 1998.

tion periods describe generalized durations of exposures that deployed forces may encounter. This grouping provides a systematic means of focusing research. For example, primary focus will first be to identify low-level concentrations and associated effects for temporary exposures, as this is the most probable exposure duration anticipated for deployed forces. Short-term exposure durations may also be anticipated and, therefore, would be considered within the research strategy. Long-term exposures to chemical agents, however, are relatively unlikely to occur and would, therefore, be of lower priority when considering research needs. This is supported by existing doctrine in which the time period of interest used by NBC planners is generally between 6 and 48 hours.[7]

> Temporary Exposure Duration: an exposure that reflects a brief, one-time or continuous occurrence. Such an occurrence may only last minutes or up to a few hours.
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> Short-term Exposure Duration: In general, this term applies to exposures that exceed the "temporary" duration and continue daily up to a two-week period. This includes continuous exposures and repeated, intermittent exposures.
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> Long-term Exposure Duration. Long-term exposures include continuous exposures or repeated, intermittent exposures that continue daily for more than a 2-week duration.

I.B.3. Effects of Low-Level Exposures. There are limited data on actual low-level exposures to CWAs. A key reason that such information is lacking is the basic means by which most toxicology research is conducted. Exposure of experimental animals to toxic agents in high doses is a necessary and valid method of discovering possible hazards in humans. Obtaining statistically valid results from small groups of animals requires the use of relatively large doses so that the effect will occur frequently enough to be detected and studied. For example, an incidence of a serious toxic effect as low as 0.1 percent would represent 2,000 people in a population of 2 million. Detecting this low incidence in experimental animals directly would require a minimum of 30,000 animals.[8] For this reason, large doses are administered to relatively small groups, and then toxicological principles are used to extrapolate the results to estimate the risk at low levels. Complications or errors may be introduced when testing interactions of low-levels of CWAs with other chemicals if the low-level effects for these other chemicals are based on extrapolation from high-level effects.

For a given chemical, low-level exposures include exposure to a given concentration for a given duration below which no significant adverse health effects (immediate or delayed) are presumed to occur in accordance with the best available scientific data. Determination of an exposure level that does not result in adverse health effects may be complicated by the nature of the pathological sequelae following intoxication.

If a temporary chemical exposure results in an immediate effect, the relationship between the exposure level and the physiological impairment may be readily determined and portrayed in a dose-response relationship. However, a single or repeated exposure to a toxicant may cause cellular damage that is not reflected as overt pathology for days, weeks, or years following the

[7] Field Manual 3-4, *NBC Protection*, Headquarters, Department of the Army, 21 February 1996, p. 3-2.
[8] Kodell, R.L., *et al*. *Fundamentals of Applied Toxicology*, Jul–Aug 1983, 3:3a–8a.

toxic exposure. Such pathological sequelae are difficult to link quantitatively to toxicant exposure. Further, under circumstances where the physiological damage is reversible, the resulting adverse health consequences will also reverse at some time after the toxic chemical exposure is stopped, leading to observations of immediate, transient adverse health effects and/or delayed, transient adverse health effects. If sufficient transient damage accumulates to cause irreversible deterioration or if the cellular pathological effects of exposure are irreversible, temporary or short-term chemical exposure may result in permanent, chronic illness. Thus, adverse health effects following a chemical exposure may be a mix of immediate, delayed, transient, or chronic symptoms and each symptom may have a different characteristic chemical exposure level.

In addition to identifying and prioritizing research areas, DoD's Research Plan will identify procedures for implementation and coordination of the Plan. On 11 November 1998, President Clinton directed the Secretaries of the Departments of Veterans Affairs, Defense, and Health and Human Services to establish a Military and Veterans Health Coordinating Board (MVHCB) as a permanent interagency body to ensure coordination on a broad range of health-related issues for military service members and veterans of military service. The MVHCB will provide recommendations to DATSB(CBD) on implementation of recommendations in Presidential Review Directive 5, Planning for Health Preparedness for and Readjustment of the Military, Veterans, and Their Families after Future Deployments[9] and provide as appropriate recommendations to establish a task force to provide interagency coordination for initiatives which include other Federal Organizations that share similar concerns and data needs. In order to fully implement the recommendations of the Strategy, DoD is to be represented on the MVHCB.

I.C. <u>SCOPE.</u> The DoD strategy for chemical warfare defense is structured around six major program areas governing overall protection of military personnel. Together, these program areas (shown in Table 1) comprise the necessary information to permit appropriate risk-based decision making that will guide policy and doctrine modification.

As stated in the objectives of P.L. 105-261, DoD policies and doctrine will require a <u>balance</u> between *providing adequate protection* <u>and</u> *avoiding any low-level exposure to chemical warfare agents*. One of the goals of proposed and ongoing research will be to establish scientific criteria which define the lowest levels that personnel may be exposed to CWAs without measurable biomedical effects. A quantitative limit for "low-level" is not specifically defined. However, a quantitative range may be assumed.[10] The upper boundary of low-level exposure will be levels "*not sufficient to endanger health immediately*."[11] This quantitative range is illustrated for the nerve agent sarin (GB) in Figure 1. As shown, there is a significant quantitative range for low-levels.

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[9] National Science and Technology Council Report, Presidential Review Directive (PRD)-5, *Planning for Health Preparedness for and Readjustment of the Military, Veterans, and Their Families after Future Deployments*, August 1998.

[10] "Low-level" has been used with multiple meanings. In this report, "low-level" refers to a quantitative dose level. The phrase "low level" also has been used in numerous reports, briefings, and publications with an entirely different meaning, and should not be confused with the definition used in this report. In the context of "low level chemical warfare," the term "low level" refers to the scale or intensity of the conflict, not the amount of chemical agent used. Thus, the *Aum Shinrikyo* attack in the Tokyo subway in March 1995 was a low level chemical attack (*i.e.*, it was not a major theater war), that involved a gradient of exposures ranging from high- to low-levels of chemical agent, which killed 12 and injured thousands.

[11] P.L. 105-261, Sec. 247, Para(b)(2)(A).

Proportionally similar values exist for most CWAs. No fixed quantitative level is appropriate for all operational scenarios.

Table 1. DoD Program Areas to Address Low-Level Exposures

Program Area	Description of Primary Activities
Hazard Identification and Assessment	– Identify and prioritize contaminants/hazards of concern – Identify concentrations/levels of concern – Identify duration and routes of exposure – Identify potential sources of exposure – Assess effects of exposure at various concentrations and durations (*e.g.*, biomarkers)
Protection	– Identify requirements for adequate personal protective measures (*e.g.*, masks, suits) – Identify requirements for physical preventive measures to reduce exposures/susceptibility – Identify requirements for medical measures to reduce susceptibility (*e.g.*, prophylactics)
Decontamination	– Identify requirements to reduce or eliminate contamination – Identify requirements for dewarning (*i.e.*, removal of contamination)
Detection	– Identify requirements for monitoring, alarm, and confirmation systems – Identify requirements for identifying pertinent diagnostic techniques (*e.g.*, biomarkers)
Surveillance	– Identify requirements for data information collection regarding exposures – Identify requirements for appropriate recording, reporting, and evaluation to identify potential effects and necessary corrective actions
Policy, Procedure, and Review	– Integrate new data into policies, doctrine, procedures, and training (as required) – Ensure review, participation, partnership with other agencies/organizations – Ensure data are collected on health effects/outcomes

A specific low-level limit is likely to be determined based on the risk a commander is willing to accept based on mission requirements. Policy and doctrine will provide the framework within which a commander makes risk decisions. As policy and doctrine evolve to address low-level exposures specifically, commanders will be provided risk assessment tools providing guidance defining various risk levels (negligible through extremely high risk), and information on who has the authority and responsibility to make risk decisions. Policy and doctrine will not arbitrarily dictate either the number or percentage of casualties that a commander can or should accept in order to complete a mission. The specific risk that will be accepted will be determined by the commander(s) based on the situation and mission requirements. Existing service policy and doctrine already establishes the framework that military commanders use to make risk decisions. This framework, known as operational risk management (ORM), is instituted within military decision making.[12] Ongoing initiatives are now establishing an ORM framework specific to assessing chemical exposure risks.[13]

[12] Key documents that provide ORM guidance include U.S. Army Field Manual (FM) 100-14, *Risk Management*, Air Force Instruction (AFI) 91-213, *Operational Risk Management (ORM) Program*, Air Force Pamphlet (AFPAM) 91-215, *Operational Risk Management (ORM) Guidelines and Tools*, and OPNAV Instruction 3500, *Operational Risk Management*.

[13] U.S. Army Center for Health Promotion and Preventive Medicine (CHPPM), Technical Guide (TG) 230(A), *Short-term Chemical Exposures Guidelines for Deployed Military Personnel*, Draft, May 1999.

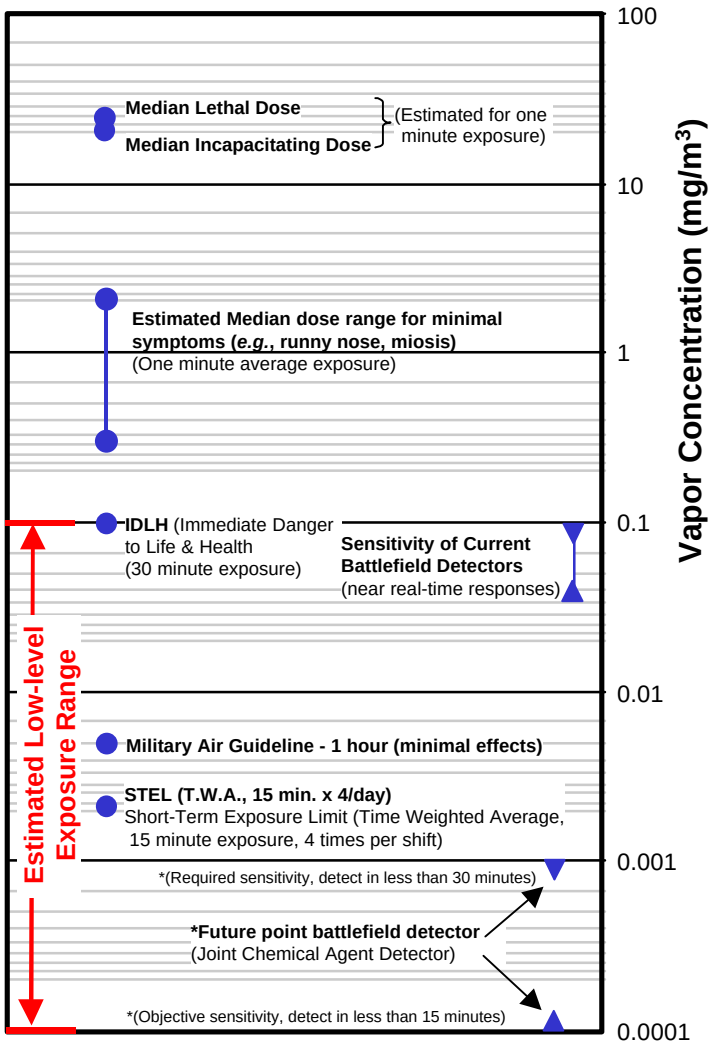

Figure 1. Quantitative Range of Temporary Exposures for the Nerve Agent Sarin (GB)

Sources:

- Levels for median lethal dose, median incapacitating dose, and minimal symptoms are for vapors (inhaled) and are derived from National Academy of Sciences (NAS), *Review of Acute Human-Toxicity Estimates for Selected Chemical-Warfare Agents*, (Washington, D.C.: National Academy Press), 1997. The NAS noted that the lethal and incapacitating doses should be lowered and the minimal effects levels should be raised, but more research is needed.
- IDLH levels are values defined by NIOSH for certain chemicals that represent the maximum concentration from which, in the event of respirator failure, one could escape within 30 minutes without a respirator and without experiencing any escape-impairing (*e.g.*, severe eye irritation) or irreversible health effect. The IDLH level corresponds to the Military Air Guideline - 1 hour (Severe effects).
- STEL levels are values defined by NIOSH as a time weighted average that should not be exceeded for any 15 minute period during a working shift (*i.e.*, 8 hours)
- The Military Air Guideline - 1 hour (minimal effects) level is derived from U.S. Army Center for Health Promotion and Preventive Medicine, Technical Guide 230A, *Short-Term Chemical Exposure Guidelines for Deployed Military Personnel* (Draft), May 1999.
- Sensitivity of current battlefield detectors include the following detection systems: M8A1 Automatic Chemical Agent Alarm, M21 Remote Sensing Chemical Agent Alarm (RSCAAL), M22 Automatic Chemical Agent Detection Alarm (ACADA), Improved Chemical Agent Monitor (ICAM),and the M256A1 Chemical Agent Detector Kit.
- Values for the sensitivity levels for the Joint Chemical Agent Detector (JCAD) are derived from the JCAD Operational Requirement Document (ORD), 23 January 1997.

A risk-based definition is appropriate to the scope of research that is planned or proposed. Research will focus on the effects of low-level exposures "*to provide solutions for the concerns and mission requirements that are specifically applicable for one or more of the Armed Forces in a protracted conflict when exposures to chemical agents could be complex, dynamic, and occurring over an extended period.*"[14] Thus, policy and doctrinal changes, as well as the material solutions from the chemical defense programs, will focus on providing adequate protection of operationally deployed military personnel from exposure to chemical warfare agents, including low-level exposures. Deployed personnel would include those in combat roles as well as combat support and combat service support roles.

Military forces generally are more physically fit than the general civilian population. With this in mind, the goal of the proposed DoD strategy is to provide for protection and detection and surveillance capabilities for low-level exposures that are appropriate for the general *military* population (*i.e.*, healthy adults of 18-55 years of age) for a variety of deployment scenarios. Specifically, low-level concentrations will be derived in a manner consistent with the approach used to establish national guidelines for the general populations for comparable types of exposure durations for other toxic industrial compounds. As a result, the research may provide dual-use applications (*i.e.*, both for military as well as civilian applications).

The proposed DoD Strategy and resulting 5-year Research Plan is designed to yield data that will guide the potential evolution of existing policies and doctrine on exposures to CWAs. These data also will be used to develop new risk management guidelines, instruments, and analytical methods with respect to such exposures, as required. The following are key elements of the DoD strategy:

(1) As there are shortfalls in information regarding the effects of CWAs at higher concentrations as well as long-term exposure durations, research on effects at these concentrations and durations may be necessary prior to lower level exposure studies.

(2) Though CWAs will be the primary focus, research will identify and address other potentially hazardous exposures that may occur concurrently with CWA exposure.

(3) The research initially will focus on knowledge gaps primarily associated with hazard identification such as toxicology-related research and model development. However, all program areas addressing chemical defense issues are critical to the success of this strategy and will be integrated into planning oversight and execution.

[14] P.L. 105-261

ANNEX TO SECTION I: Toxicology and Chemical Agent Exposures

This Annex expands on some of the information already presented in Section I. It provides information that details aspects of the scope and limitations of the proposed research efforts and potential changes to policy and doctrine. Specifically this Annex provides answers to the following questions:

- What are the characteristics of exposures to CWAs (concentration, route, and duration) for military personnel on the battlefield?
- What are the effects of exposures to CWAs (Operational significance? Occupational significance?) for military personnel during and after battlefield operations?
- What are the key differences between the laboratory and the battlefield in defining potential hazards and in developing responses?

Characteristics of Exposure[15]

To characterize fully the potential hazard of a specific chemical agent, information is needed not only on the type of effect a chemical agent produces and the dose required to produce that effect but also information about the agent, the exposure, and the disposition by the subject. Adverse or toxic effects in a biological system are not produced by a chemical agent unless that agent (or its metabolic products) reaches target sites in the body *at a concentration* and *for a length of time* sufficient to produce a toxic manifestation. The major factors that influence toxicity as it relates to exposure for a specific chemical are the *route of administration* for a specific chemical, the *duration and frequency of exposure*, and the *concentration of the chemical exposure*. Chemicals are typically considered effective as warfare agents not only because of their extreme toxicity but also because they effectively enter the body through various routes (especially through the skin in addition to inhalation.)

Route of Exposure. Routes (pathways) by which toxic agents gain access to the body are the lungs (inhalation), skin (topical, percutaneous, or dermal), and gastrointestinal (ingestion), among others. Chemicals generally produce their most toxic effect and most rapid response when given directly into the bloodstream (that is, intravenously). Identification of the route(s) of exposure for a toxic substance often provides useful information about its extent of absorption and potential effects. Occupational exposure to toxic agents most frequently results from breathing contaminated air (inhalation) or direct and prolonged contact with the substance (percutaneous absorption). Exposure to low-levels of volatile CWAs in a battlefield environment would almost certainly occur by inhalation of agent vapors. Vapor inhalation is the primary route of concern since the toxicity is significantly greater via inhalation than via the skin.[16] Inhalation causes greater toxicity because it is a more direct route to the bloodstream, thus enhancing systemic distribution.

[15] For an excellent source of information on how various substances cause toxicity, see *Casarett and Doull's Toxicology: The Basic Science of Poisons* (5th ed.), Curtis D. Klaassen, editor (McGraw-Hill: New York), 1996.
[16] For example, sarin (GB) is at least 20 times more toxic via inhalation than percutaneously.

Duration and Frequency of Toxic Exposure. The duration and frequency of exposure to an agent is also a critical factor in determining its toxicity. As defined earlier, there are three categories for the duration of exposure: (1) temporary exposure, (2) short-term exposure, and (3) long-term exposure. For many agents, the toxic effects that follow a single exposure are quite different from those produced by repeated exposure. Temporary or short-term exposure to agents that are rapidly absorbed is likely to produce immediate toxic effects but also can produce delayed toxicity that may or may not be similar to the toxic effects of long-term exposure. Conversely, long-term exposure to a toxic agent may produce some immediate effects after each exposure in addition to the long-term effects.

The other time-related factor that is important in the characterization of exposure is the frequency of exposure. The frequency of exposure must be compared to the rate of elimination of the agent from the body. If the body eliminates a toxic agent rapidly, a chemical that produces severe effects with a single exposure may have no effect if the same cumulative exposure is spread out over several intervals. Of course, residual cell or tissue damage may occur with each dose even though the chemical itself is not accumulating. The important consideration, then, is whether the interval between exposures is sufficient to allow for complete repair of cell or tissue damage. With any type of multiple exposure the production of a toxic effect may not only be influenced by the frequency of administration but may, in fact, be totally dependent on the frequency rather than the duration of exposure. Long-term toxic effects may occur, therefore, if the chemical accumulates in the biological system, if it produces irreversible toxic effects or more toxic metabolites, or if there is insufficient time for the system to recover from the toxic damage within the exposure frequency interval.

Concentrations of Chemical Exposures: The Laboratory vs. The Battlefield. The Department of Defense has conducted extensive tests and analyses on the effects of various CWAs. Historically these tests have focused on the effects of CWAs at concentrations known to cause performance degradation of its forces during operations. Testing for long-term and low-level exposures has required innovative techniques to determine the effects of these exposures scientifically.

Generating reproducible and consistent low-levels of CWAs *by themselves* is extremely difficult in a battlefield (or any outdoor) environment since agent behavior will be affected by many factors including weather, topography, vegetation, and soil.[17] Since the generation of low-levels of CWAs without concurrent generation of high levels of CWAs is highly unlikely, doctrine may be adapted to focus on locating the source(s) of CWAs if low-levels are detected. In the laboratory, low-levels of CWAs may be generated and their effects analyzed in a reproducible and consistent manner. As illustrated in Table 2, laboratory conditions will not provide an accurate representation of low-level exposure conditions that may occur on a battlefield. However, laboratory tests may provide a benchmark to estimate low-level effects on the battlefield, though caution will be taken in extrapolation results from the laboratory to the battlefield.

[17] The complex behaviors of chemical agents in the environment are detailed in U.S. Army Field Manual (FM) 3-6, *Field Behavior of NBC Agents*, Chapter 1, "Chemical Agents," 3 November 1986.

Table 2. Laboratory *vs*. Battlefield Exposures

Condition	Laboratory	Battlefield
Weather (wind, humidity, temperature, air stability, precipitation)	Controlled, simple	Uncontrolled, complex
Sunlight	Artificial or none	Present (variable)
Topography	Fixed, simple	Variable, complex
Vegetation/Soil	None	Varieties present
Chemical State	Vapors, aerosols, and liquids (pure)	Vapors, aerosols and liquids (likely to be contaminated)
Rate of exposure	Intermittent, continuous and sustained	Variable and intermittent
Personnel	None exposed; animal models used	Personnel exposed and stressed (physiologically and psychologically)

A key challenge for the scientific community is to develop a valid methodology and appropriate toxicological principles for predicting dose-response effects for CWAs over longer exposure times and at lower concentrations. A valid methodology requires developing techniques that are verifiable and defensible by the scientific community for maintaining and accurately measuring agents in a test chamber. To date, researchers have encountered technological challenges in both (1) generating constant low-levels of chemical agents for long exposure periods (hours), and (2) developing sampling and analysis methods to verify low-level exposure concentrations within a test chamber throughout the exposure period. While researchers will likely be able to overcome these challenges, these challenges indicate that generating low-level and/or long term exposures to CWAs on the battlefield will be extremely difficult *without concurrently generating high levels of agent*. Table 3 illustrates the scenarios in which personnel are likely to be exposed to low-levels of CWAs. Ongoing and proposed research identified in section IV of this report is intended to identify the effects of such exposures.

Table 3. Typical Scenarios for Potential Battlefield Exposures to Low-levels of CWAs.

- Downwind hazard from adversary's attack with CWAs.
- Collateral damage of adversary's chemical weapons storage facility/depot (or chemical industrial facility) and resulting dispersal of agent and downwind hazard.
- Off-gassing of vapors from equipment, material, and surfaces in a previously contaminated area.

Interaction of Chemicals

One of the most complex tasks in toxicology is to determine the toxic effects resulting from the interaction of two or more different compounds on the human body,[18] or *mixtures toxicology*.[19] Irrespective of the route of exposure of other potential environmental hazards, mixtures toxicology involving CWAs is complex since such studies would require inhalation tests.[20] Inhalation tests require special test facilities. Within the United States, there are very few inhalation test chambers that have the required safety protection features necessary for tests involving CWAs. Thus, the number of facilities is a limiting factor for both the number of tests that can be performed at any one time and the expense of these types of tests compared with the expense of tests that examine exposure by other routes.

Another limiting factor in conducting mixtures toxicology is the theoretically infinite number of potential combinations of compounds that might be studied.[19] It may be possible to study the effects of two or three compounds in combinations, though multiple mixtures tests could become prohibitively expensive. (See also Table 9 in Section IV of this report.) The effects of exposure to two or more chemicals simultaneously may produce a variety of potential responses, as illustrated in Table 4. The specific interaction between CWAs and other compounds would need to be determined empirically. However, some predictive modeling could suggest likely interactions. For example, compounds that share the same structure activity relationship may be additive. Thus, exposure to two cholinesterase inhibitors (*e.g.*, sarin and VX) would be predicted to have additive effects.

[18] No chemical defense testing involves the exposure of human subjects to chemical warfare agents. Any use of human subjects in testing would require full compliance with the "Common Rule," Federal Policy for the Protection of Human Subjects, Food and Drug Administration regulations, Federal Acquisition Regulations, DoD Directives and Instruction, and *all* other applicable laws, regulations, issuances, and requirements.

[19] Almost all toxicological research has focused on the single chemical, or in limited cases, two or three chemicals in combination. However, in the real world, individuals routinely encounter many complex chemical mixtures. These chemical mixtures are rarely addressed in research. Systematic toxicity testing of chemical mixtures is highly impractical because of the immense number of mixtures involved. For example, a 25-chemical mixture (*e.g.*, cigarette smoke) has 2^n - 1 or 22,554,431 combinations at one concentration per chemical. A very conservative estimated cost of $100,000 for a 13-week toxicity study with a single species of rodent according to the National Toxicology Program protocol translates into more than $3 trillion for all the combinations, at one concentration per chemical, in a 25 chemical mixture. See Yang, R.S.H., ed., *Toxicology of Chemical Mixtures: Case Studies, Mechanisms, and Novel Approaches* (San Diego: Academic Press), 1994. Another recent work addressing the difficulty in assessing this problem is Nicholas Ashford and Claudia Miller, *Chemical Exposures: Low levels and high stakes* (2nd ed.), (New York: John Wiley & Sons, Inc.), 1998.

[20] Low-levels of volatile CWAs would almost certainly be encountered as vapors and would be most toxic (by at least an order of magnitude more toxic than by other routes of exposure) when inhaled, hence inhalation test would most likely yield the most beneficial data. See also discussion on page 10.

Table 4. Effects of Chemical Interactions

Type of Interaction	Description
• Additive	Combined effect equals the sum of the effects of the compounds separately
• Synergistic	Combined effect is greater than the sum of the effects of the compounds separately
• Potentiation	When one substance does not have a toxic effect, but when added to another chemical makes that chemical much more toxic
• Antagonism	
– Functional Antagonism	When two chemicals counterbalance each other by having opposite effects on the same system
– Chemical Antagonism	When two chemicals react with each other to produce a less toxic product
– Dispositional Antagonism	When the disposition (*i.e.*, absorption, biotransformation, distribution, or excretion) of a chemical is altered so that that concentration and/or the duration of the chemical within the body are diminished
– Receptor Antagonism	When two chemicals competitively bind to the same receptor diminishing the toxic effect (also referred to as blockers)

> ***"There's no such thing as a risk free military operation."***
> *Chairman of the Joint Chiefs of Staff,*
> *General Henry H. Shelton, March 24, 1999*

SECTION II: Review of Current Policy, Doctrine, and Guidance

This section highlights current policy, doctrine, and guidance that may have direct or indirect applicability to addressing the potential hazards from exposures to low-levels of chemical warfare agents. A broad scope of existing and draft documents are included in this review. Sources of information include, but are not limited to, applicable DoD directives and instructions joint publications, Service field manuals, pamphlets, and warfighting publications, U.S. Army Center for Health Promotion and Preventive Medicine (CHPPM) technical guides, and various publications from the National Research Council. Technical programs and efforts that examine low-level chemical exposures are also categorized in this review.

Table 5 (pages 18-20) provides an extensive, though not exhaustive, list of documents to include in the review. Documents referenced in Table 5 can be categorized according to the general type of guidance that the document may provide.[21] Guidance includes operational, occupational, and scientific/research guidance, which are defined as follows:

- *Operational guidance*~~gu~~idance that examines operationally significant levels appropriate for personnel involved in a military operation in which the environment is uncontrolled or irreversible. These levels are based upon the assumption that military personnel are healthy and between the ages of 18~~5~~5. Unlike occupationally significant levels, once the limit for safe exposure is reached, operations do not end or personnel may not be re-deployed to safe area.
- *Occupational guidance*~~gu~~idance that indicates occupationally significant levels appropriate for industrial workers within a controlled environment. These levels are based upon an eight-hour work day. When the limit for safe exposures has been reached, engineering and administrative controls or personal protection may be utilized, workers may be assigned to a safer environment, or operations cease.
- *Scientific/Research guidance*~~hig~~hlights ongoing technical efforts that may be relevant to low-level chemical exposures. Data from scientific and research efforts may serve to drive operational and occupational guidance.

Within each of the guidance categories, documents may be further grouped into categories based on the level of exposure referred to in the document~~na~~mely, temporary, short-term, or long-term exposure.

The majority of the operational guidance is applicable only to temporary exposures, with some short-term exposure scenarios addressed. Guidance dealing with long-term exposures to low-levels of chemicals~~wh~~ile essentially non-existent for operational scenarios~~do~~es exist to

[21] Some documents may apply to more than one category, but they are listed only once to prevent redundancy.

address such potential exposure scenarios in the occupational or general population setting. Efforts are underway in the scientific and technical arena to obtain additional data on potential short-term and long-term operational exposures that may eventually serve to drive new policies in this area. Following are selected extracts and examples from existing guidance and doctrine, each of which may be revised based on the results of research.

Several documents provide guidance for the documentation and surveillance of the health of deployed military personnel in relation to an associated health risk, including possible exposure to a chemical warfare agent.[22] Ideally health data is recorded before, during, and after deployment.[23] The health data collected before a deployment provides a baseline reading for the personnel within a particular command and is compared to the health data obtained during deployment to help identify unknown exposures or trends. Also during a deployment, an analysis of the environment is utilized to uncover health threats that are present.[24] The spectrum of collected data is recorded and analyzed, converted into a health risk assessment, and fed into a commander's overall risk assessment.[25] The purpose of this health risk assessment is to "ensure that personnel accept no unnecessary health risks."[26] When known exposures cannot be avoided, the event is recorded for later evaluation and reference. In the event of an anticipated exposure, accurate documentation of exposure and appropriate follow-up will be a high priority goal.[27] While existing guidance does not focus specifically on CWA exposures, it includes CWAs in the list of health threats included in a health assessment.

Existing doctrine[28] revealed that actions and measures taken against exposures to CWAs are based in part upon the type of chemical employed and a risk assessment. When non-persistent agents are employed, troops will remain in the environment under the assumption that the threat will be reduced in a matter of minutes; when semi-persistent or persistent agents are employed, exposure hazards will exist longer requiring more extensive use of decontamination, avoidance, and protection.[29] At the same time, the commander will weigh the risks associated with operations in a contaminated environment against the risks associated with moving the operations into a contamination-free environment. According to TRADOC PAM 525-20:

> Consideration is given to the tactical situation, the protection provided by his present position, the increased exposure to the hazard incurred by relocation, the possibility of further NBC attacks, and the impact of continuing to fight in partial or full protection. If the contamination hazard can be circumvented, adjusted to, or minimized, the decision is made to stay and fight and decontaminate later.[30]

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[22] See for example, DoD Directive 6490.2, *Joint Medical Surveillance*, 30 Aug 1997; DoD Instruction 6490.3, *Implementation and Application of Joint Medical Surveillance for Deployment*, 7 Aug 97; and CJCS Memorandum MCM-251-98, *Deployment Health Surveillance and Readiness*, 4 Dec 98.
[23] DoD Directive 6490.2, p. 3.
[24] *Joint Service Instruction On Deployment Health Surveillance and Protection* (DRAFT). Secretaries of the Army, Navy, and Air Force, 1999: pp. 11-12.
[25] *Ibid*. p. 14.
[26] *Ibid.*
[27] *Ibid*. p. 16.
[28] Many doctrine references provided in Table 5 are U.S. Army and U.S. Marine Corps doctrine documents and may not apply to other Services' chemical defense doctrine. They do, however, exemplify some approaches to dealing with exposures to CWAs. DoD is continually moving towards developing multi-service and joint doctrine.
[29] TRADOC PAM 525-20, *US Army Operational Concept for Individual and Collective Measures for Chemical, Biological, and Radiological (CBR) Defense*, Headquarters Department of the Army, 30 July 1982.
[30] *Ibid*.

As alluded to above, when full protective posture is employed, consideration must be given to the risks associated with fatigue and heat exposures. FM 3-4 states that the objective is to have no more than 5 percent casualties as a result of heat exposure from protective equipment.[31] No statements in doctrine identify an objective for allowable, acceptable, or other casualty levels as a result of exposures to chemicals.

The risk of casualties within a chemical environment depends mainly upon the concentration of the agent and the extent of protection. Non-persistent agents present a low risk to personnel in full protection gear. Persistent agents also present a low or negligible risk if decontamination measures are performed quickly and correctly.[32] Readings on the Chemical Agent Monitor (CAM) describe the levels of contamination. A reading between 0 and 1 bars is generally an acceptable level.[33] A moderate contamination level occurs when the reading is between 1 and 4 bars. FM 3-3 defines moderate contamination as "one gram of agent per square meter."[34] Readings between 5 and 8 bars are considered to be heavy contamination. FM 3-3 defines heavy contamination as "ten grams or more of agent per square meter."[35]

Within a contaminated environment or an environment in which chemical agents are employed, the doctrine highlights the planned duration of the mission. Doctrine considers vaporized chemicals to be a short term problem and solid and liquid chemicals to be a long-term problem.[36] Generally, the duration of a low-level operational exposure does not extend past one or two days. The time-period of interest used by NBC planners is generally between 6 and 48 hours. For planning purposes, durations of less than six hours are not explored.[37]

In addition to chemical concentrations and durations, doctrine provides guidance to minimize effects of chemical exposures to operations. Doctrine sets forth that a chemical environment should only invoke minimal degradation to U.S. operations and forces.[38] According to FM 3-5, "[t]he objective is to reduce the level of contamination to regenerate needed combat power. Therefore, the unit is able to sustain its mission in a contaminated environment."[39] If NBC defense plans are not implemented correctly, mass casualties are likely to occur. Assuming a thoroughly prepared and rehearsed NBC defense plan is implemented, the minimum anticipated impact from NBC hazards is a temporary reduction in the operational tempo for affected forces.[40]

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[31] Field Manual (FM) 3-4, *NBC Protection*, 28 October 1992: p. 2-6.
[32] FM 3-5, *NBC Decontamination*, 1996: p. 4.1.
[33] *Ibid*. Readings are semi-quantitative values. Because agent concentration varies from one spot to another depending upon wind velocity and other environmental factors, numerical displays of agent concentration in typical units would be impractical and unreliable. Accordingly, the CAM display warns of a low vapor hazard (1 - 3 bars visible), a high vapor hazard (4 to 6 bars visible), or a very high vapor hazard (7 - 8 bars).
[34] FM 3-3, *Chemical and Biological Contamination Avoidance*, 16 November 1992: p. 1-4.
[35] *Ibid*.
[36] FM 3-100, *Chemical Operations Principles and Fundamentals*, 08 May 1999, p. 3-9.
[37] FM 3-4, *NBC Protection*. Headquarters Department of the Army, 21 February 1996, p. 3-2.
[38] Joint Pub 3-11, *Joint Doctrine for Nuclear, Biological, and Chemical (NBC) Defense*, 10 July 1995: p. viii.
[39] FM 3-5, *NBC Decontamination*, 1996: p. 4-0.
[40] FM 3-4-1, *Multiservice Procedures for NBC Defense of Fixed Sites, Ports, and Airfields*, 1998: p. 2-2.

Table 5. Elements of DoD Strategy to Address Exposures to Low-levels of CWAs.

OPERATIONAL GUIDANCE

1. U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM), Technical Guide (TG) 230(A); *Short-term Chemical Exposure Guidelines for Deployed Military Personnel*; draft (May 1999).
2. U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM), Technical Guide (TG) 230(B); *Long-Term Chemical Exposure Guidelines for Deployed Military Personnel (forthcoming).*
3. Joint Publication 3-11 *Joint Doctrine for Nuclear, Biological, and Chemical (NBC) Defense*, 10 July 1995.
4. MCM 32-99, 17 February 199, Chemical Warfare Exposure Planning Guidance [Classified SECRET.]
5. FM 3-3, *Chemical and Biological Contamination Avoidance*, Headquarters Department of the Army, Washington D.C., 16 Nov 1992.
6. FM 3-4, *NBC Protection,* Headquarters Department of the Army, Washington, D.C.; 29 May 1992.
7. FM 3-4-1, *Multi Service Procedures for NBC Defense of Fixed Sites, Ports, and Airfields*, 1998.
8. FM 3-5, NBC Decontamination, *,* Headquarters Department of the Army, Washington, D.C.; 17 November 1993
9. FM 3-6, *Field Behavior of Chemical Agents,* Headquarters Department of the Army, Washington, D.C.; 03 November 1986.
10. FM 3-7, *NBC Handbook,* Headquarters Department of the Army, Washington, D.C.; 29 September 1994.
11. FM 3-9/NAVFAC P-467/AFR 355-7, *Potential Military Chemical/Biological Agency and Compounds,* 12 December 1990.
12. FM 3-19, *NBC Reconnaissance,* Headquarters Department of the Army, Washington, D.C.; 19 November 1993.
13. FM 3-21, *Chemical Accident Contamination Control*.
14. FM 3-100, *Chemical Operations Principles and Fundamentals,* Headquarters Department of the Army, Washington, D.C.; 08 May 1996.
15. FM 3-101-2, *NBC Reconnaissance Squad/Platoon (FOX) Operations Tactics, Techniques, and Procedures,* Headquarters Department of the Army, Washington, D.C.; 10 August 1994.
16. FM 8-9, *NATO Handbook on the Medical Aspects of NBC Defensive Operations* (AMED P-6; NAVMED P-5059; AFP 161-3)
17. FM 8-10-7, *Health Service Support in a Nuclear, Biological, and Chemical Environment.*
18. FM 8-285, *Treatment Of Chemical Agent Casualties And Conventional Military Chemical Injuries.*
19. STANAG 2047. *NBC Emergency Alarms of Hazard or Attack*.
20. STANAG 2917. *Chemical Casualty Assessment Exercise*.
21. NATO short-term field drinking water standards [Standardization Agreements (STANAG)] (page 16 of TG 230A).
22. Compounds classified per ACE Policy for Defensive Measures against Toxic Industrial Chemical Hazards during Military Operations (NATO/PFP 1996). (page C-12 of TG 230A)
23. Department of the Army Pamphlet 50-6, Update, *Chemical Agent Incident Response and Assistance (CAIRA) Operations,* 17 May 1991.
24. Technical Bulletin, Medical 577, *Sanitary Control and Surveillance of Field Water Supplies*, (DRAFT), June 1996.
25. AR 350-42, *Nuclear, Biological and Chemical Defense and Chemical Warfare*.
26. TRADOC PAM 525-20, 30 July 1982. US Army Operational Concept for Individual and Collective Measures for Chemical, Biological, and Radiological (CBR) Defense.
27. TRADOC PAM 525-48, 20 December 1985. US Army Operational Concept for Logistics Support in a Nuclear, Biological, and Chemical (NBC) Environment.
28. Field Manual 100-14, *Risk Management*; Headquarters Department of the Army, Washington D.C.; 23 April 1998.
29. Defense Intelligence Report, DI-1816-8-99, January 99—Medical Intelligence Assessment of Deployment Environmental Health Risks.
30. House of Representatives Bill HR 4036, Persian Gulf War Veterans Health Act of 1998.
31. National Research Council, 1995. *Guidelines for Chemical Warfare Agents in Military Field drinking Water*. Committee on Toxicology, National Academy Press, Washington D.C.
32. FM 20-400. *Military Environmental Protection.* 1997 (draft).
33. Joint Publication 4-02, *Doctrine for Health Service Support in Joint Operations* (page 5-2).
34. NATO Work Groups: NBC Defense Working Group; NBC Medical Working Group; Land Group 7 (LG.7)—Joint NBC Defense; Challenge Subgroups—Chemical/Biological Toxicity Challenge Levels; General medical Working Party, Aeromedical Working Group; Research Technology Area/Human Factors Medical (RTA/HFM) Panel NB&C Medical Subgroups
35. Marine Corps Warfighting Publication (MCWP) 3-37, *Marine Air Ground Task Force (MAGTF) NBC Defense*.
36. Army regulation 350-41, *Training in Units* (page 5-4).
37. DoD Directive 6025.3, *Clinical Quality management Program in the Military Health Services* (page 5-15).
38. DoD Instruction 1322.24*, Military Medical Readiness Skill Training* (page 5-15).
39. Air Force Manual (AFMAN) 32-4019, *Chemical-Biological Warfare Commander's Guide*—includes the Vulnerability Assessment Tool and new consequence management requirements (page 5-28).

Table 5. Elements of DoD Strategy to Address Exposures to Low-levels of CWAs. (continued)

40. National Science and Technology Council Report, Presidential Review Directive (PRD)—5, Planning for Health Preparedness for and Readjustment of the Military, Veterans, and Their Families after Future Deployments, August 1998.
41. Institute of Medicine, *Health Consequences of Service During the Persian Gulf War, Recommendations for Research and Information Systems*, 1996.
42. (Army Programs/Training: Combined Arms in a Nuclear/Chemical Environment (CANE), and Physiological and Psychological Effects of the NBC Environment and Sustained Operations on Systems in Combat (P2NBC2).)
43. U.S. Army Center for Health Promotion and Prevention Medicine (USACHPPM), Technical Guide (TG) 231—describes field occupational hazards from chemicals.

OCCUPATIONAL GUIDANCE

44. National Research Council, *Toxicity of Military Smokes and Obscurants, Vol. 1.* Committee on Toxicology, National Academy Press, Washington D.C., 1997.
45. National Research Council*, Emergency and Continuous Exposure Limits for Selected Airborne Contaminants*, National Academy of Sciences. AD-A142-133, Vols. 1-3, 1984.
46. American Industrial Hygiene Association, *Emergency Response Planning Guidelines,* AIHA Press, Fairfax, VA, 1997.
47. National Research Council (NRC). 1986. *Criteria and Methods for Preparing Emergency Exposure Guidance level (EEGL), Short-term Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance Level (CEGL) Documents.* Committee on Toxicology, National Academy Press, Washington D.C.
48. National Research Council (NRC), *Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants,* Volume 7, 1986. Committee on Toxicology, National Academy Press, Washington, DC.
49. National Research Council, 1993. *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances*. Committee on Toxicology, National Academy Press, Washington D.C.
50. Environmental Protection Agency. 1997, *National Advisory Committee for Acute Exposure Guidelines Levels for Hazardous Substances (DRAFT);* Federal Register, Thursday, 30 October.
51. California Environmental Protection Agency. 1995, *The Determination of Acute Toxicity Exposure Levels for Airborne Toxicants,* Office of Environmental Health Hazard Assessment, January.
52. American Conference of Governmental Industrial Hygienists. 1996, *Threshold Limit Values for Chemical Substances and Physical Agents,* ACGIH Press, Cincinnati, OH.
53. American Conference of Governmental Industrial Hygienists (ACGIH). 1991. *Documentation of the Threshold Limit Values and Biological Exposure Indices.* Sixth Edition, Vols I-III., ACGIH, Cincinnati, OH.
54. USACHPPM, Directorate of Toxicology, Health Effects Program, *Determination of One-Hour Acute Inhalation Risk Values Protective of the General Population Concerning Products of Incomplete Chemical Warfare Incineration: A Re-evaluation,* March 1986, Aberdeen Proving Ground, Edgewood, Maryland.
55. Agency for Toxic Substances and Disease Registry (ATSDR). 1997. *Toxicological Profiles*. U.S. Public Health Service (CD-ROM). CRC Press, Baton Rouge, LA.
56. American Industrial Hygiene Association (AIHA). 1997. *Odor/Thresholds for Chemicals with Established Occupational Health Standards,* 1989. AIHA, Akron, Ohio.
57. National Institute of Safety and Occupational Health (NIOSH) Pocket Guide. (page C-12 of TG 230A)
58. Department of the Army Pamphlet 40-8, Occupational *Health Guidelines for the Evaluation and Control of Occupational Exposure to Nerve Agents GA, GB, GD, and VX,* 4 December 1990.
59. Department of the Army Pamphlet 40-173, *Occupational Health Guidelines for the Evaluation and Control of Occupational Exposure to Mustard Agents H, HD and HT,* 30 August 1991.
60. Environmental Protection Agency, EPA 822-R-96-001, *Drinking Water Regulations and Health Advisories,* Office of Water, United State Environmental Protection Agency, October 1996.
61. National Library of Medicine's Hazardous Substance Database (HSDB). (page C-12 of TG 230A)
62. Military forces of the U.S., Britain, Canada, and Australia in operations involving those nations should comply with short-term standards (Quadripartite Standardization Agreement (QSTAG)] of the Quadripartite Armed Forces (page 16-17 of TG 230A).
63. U.S. Tri-Service Standards (page 16-17 of TG 230A).
64. Registry of Toxic Effects of Chemical Substances. (page C-12 of TG 230A)
65. New Jersey Substance Fact Sheet. (page C-12 of TG 230A)
66. Chemical Hazard Response Information System. (page C-12 of TG 230A)
67. National Research Council, 1996. *Permissible Exposure Levels for Selected Military Fuel Vapors.* Committee on Toxicology, National Academy Press, Washington D.C.
68. Review of EPA's Environmental Monitoring and Assessment Program (three reports, 1994-1995).
69. *Hazardous Materials on the Public Lands*. 1992.
70. *Human Exposure Assessment for Airborne Pollutants*. 1991.
71. Monitoring Human Tissues for Toxic Substances. 1991

Table 5. Elements of DoD Strategy to Address Exposures to Low-levels of CWAs. (continued)

72. *Tracking Toxic Substances at Industrial Facilities.* 1990.

SCIENTIFIC/RESEARCH GUIDANCE

73. Stuempfle, A.K., Howells, D.J., Armour, S.J., and Boulet, C.A., International Task Force 25: *Hazard From Industrial Chemicals*, Final Report, ERDEC-SP-061, U.S. Army Edgewood Research, Development and Engineering Center, Aberdeen Proving Ground, MD, April 1998.
74. U.S. Army, *Information for Combat Developers on Performance Degrading Effects from Exposure to G-Nerve Agents*, 1997. Prepared by Life Systems, Inc., under Contract No. DAMD17-93 C-3006.
75. U.S. Army, *Information for Combat Developers on Performance Degrading Effects from Exposure to Mustard Agent*, 1997. Prepared by Life Systems, Inc., under Contract No. DAMD17-93-C-3006.
76. U.S. Army, *Information for Combat Developers on Performance Degrading Effects from Exposure to VX*, 1997. Prepared by Life Systems, Inc., under Contract No. DAMD17-93-C-3006.
77. (Temporary exposure—work in progress by Institute of Medicine (IOM) in which a contract research panel commissioned review standard definitions for purposes of acute studies, including duration and dose scheduling).
78. (Single event single agent exposures—work in progress by Edgewood Chemical and Biological Center in which a series of low-level toxicological studies are being conducted).
79. (Short-term exposure—work in progress by IOM in which a contract research panel commissioned to set standard definitions for subchronic studies, including duration and dose scheduling).
80. (Long-term exposure—work in progress by IOM in which a contract research panel commissioned review standard definitions for purposes of chronic studies, including duration and dose scheduling).
81. (Repeated/chronic/long-term exposures—work in progress by UMAB/USAMRICD that examines molecular targets for organophosphates in the central nervous system).
82. (Repeated/chronic/long-term exposures—work in progress by Texas Tech Univ Health Science Center that examines the cellular and molecular neuropathophysiology of subacute organophosphate CWAs).
83. (Repeated/chronic/long-term exposures—work in progress by WRAIR/USAMRICD that examines chronic effects of CWA exposure).
84. (Repeated/chronic/long-term exposures—work in progress by USAMRICD that develops an appropriate animal model to study effects of low dose chronic chemical warfare agent exposure.)
85. (Repeated/chronic/long-term exposures—work in progress by Rogene Henderson, Ph.D. Lovelace Respiratory Research Institute Albuquerque, NM that examines the long-term effects of subclinical exposures to sarin.)
86. (Single event single agent exposures—work in progress by the Military Research Institute for Chemical Defense that examines the organophosphonate cardiovascular toxicity in the open-chested porcine model.)
87. (Single event single agent exposures—work in progress by Herman vanHelden, Ph.D. Prins Maurits Lab, Netherlands that examines the low-level exposure to GB Vapor in air: diagnosis/dosimetry, lowest observable effect levels, performance-incapacitation, and possible delayed effects.)
88. (Concurrent exposures to toxic industrial compounds, preventive medicines, and battlefield chemicals—work in progress by US Army Medical Research and Materiel Command relating.)
89. (Concurrent exposures to low grade radiation, fuels, and hazards—work in progress by the Center for Health Promotion and Preventive Medicine.)
90. (Concurrent exposures to battlefield chemicals—work in progress by Medical Follow-up Agency Institute of Medicine/National Academy of Sciences.)
91. (Concurrent exposures to battlefield chemicals—work in progress by Barry W. Wilson, UC Davis.)
92. (Concurrent exposures to battlefield chemicals—work in progress by M. Abou-Donia, Ph.D., Duke University Medical Center.)
93. (Concurrent exposures to battlefield chemicals—work in progress by Satu M. Somani, Ph.D., Southern Illinois University.)
94. (Concurrent exposures to battlefield chemicals—work in progress by Carl Olson, Ph.D., Battelle.)
95. (Prevention and Protection against antidotes & prophylactics—work in progress by USAMRICD.)
96. (Decontamination—work in progress with JSMG and ECBC.)
97. (Chemical Agent alarms/sensors—work in progress by JSMG and CHPPM.)
98. (Continuous chemical agent monitors—work in progress with JSMG and TAML.)
99. (Biomarkers for CWA Exposure—work in progress by USAMRICD, TNO Prins Maritus Lab, ECBC, and JSMG.)
100. (Exposure and Effects information—work in progress by CHPPM. Health effects are also being worked by the US Army Medical Research and Materiel Command. Environmental and ecological effects by ECBC.)
101. *Toxicologic Assessment of the Army's Zinc Cadmium Sulfide Dispersion Tests.*
102. National Research Council, 1994. *Review of the U.S. Naval Medical Research Institute's Toxicology program*. Committee on Toxicology, National Academy Press, Washington D.C.
103. National Research Council, 1994. *Health Effects of Permethrin-Impregnated Army Battle-Dress Uniforms*. Committee on Toxicology, National Academy Press, Washington D.C.

SECTION III: Current FY 99 and Proposed Research Initiatives

Table 6 identifies several ongoing research initiatives that are already attempting to address existing data gaps regarding chemical hazards during deployments (in each of the program areas shown in the outline below). Some studies specifically address low-level concentrations while others are address higher-level concentrations in order to help direct future low-level studies. Some studies address individual chemicals while others examine mixtures. The studies listed are being done in all program areas described in Section I of this Strategy and are organized by program area. This is *not* an all-inclusive listing of research in this area.

RESEARCH PROGRAM AREAS

I. IDENTIFICATION
- A. Definitions
  1. Threat/Hazard
  2. Low-level exposure
  3. Long-term exposure
  4. Short-term exposure
  5. Temporary Exposure
- B. Low-level Chemical Agent Hazard Assessment
  1. Single event single agent exposures
  2. Other
  3. Repeated/chronic/long-term exposures
- C. Concurrent exposures
  1. Toxic environmental substances
  2. Low grade radiation
  3. Preventive medications
  4. Fuels
  5. Hazards

II. PROTECTION
- A. Antidotes and prophylaxes
- B. Personal protective equipment (PPE)/clothing

II. DECONTAMINATION

IV. DETECTION
- A. Chemical agent
  1. Alarms/sensors
  2. Continuous monitors
- B. Biomarkers for CWA Exposure

V. SURVEILLANCE
- A. Exposure information (recording, reporting, coordinating, retaining)
  1. Type (chemical(s)/rad)
  2. Concentration and duration
  3. Location
- B. Effects information (documenting reporting, retaining)
  1. Health effects
  2. Environmental effects
  3. Ecological effects

VI. RISK MANAGEMENT IMPLENTATION
- A. Doctrine/policy
- B. Risk communication

Table 6. Low-Level Exposures Research Program Areas
Ongoing and Planned Projects FY99, Listed by Program Area Identified in DoD Strategy to Address Low-Level Exposures

Program Area	Known work in progress/Funding Agency	Scope of Work
I. IDENTIFICATION: A. Definitions		
I.A.1 Threat/Hazard	CHPPM (draft)	Definitions-Draft Response to GAO report; introduction to DoD Strategy (Section 1)
	FM 100-14, Risk Management, 23 April 1998/U.S. Army Training and Doctrine Command	Describes 4-step process of risk management process for deployment decision-making to include first step of hazard identification (includes process for assessment of severity and probability)
	Defense Intelligence Report, DI-1816-8-99, Jan 99-Medical Intelligence Assessment of Deployment Environmental Health Risks/Epidemiology and Environmental Health Division	Establishing process to evaluate and determine environmental health risks [acute (Tier I and II) and long-term Tier III)] that may influence operational success
I.A.2 Low level exposure	CHPPM (draft)	Definitions : Proposed Strategy (Section 1) Also see TG230A (CHPPM)
	IOM Study Panel (draft)/USAMRICD	Contract research panel commissioned for review of standard definitions for low level CWA's in man and appropriate model species.
I.A.3 Long-term exposure	CHPPM	Definition (Strategy - Section 1)
	IOM Study Panel /USAMRICD	Contract research panel commissioned review standard definitions for purposes of chronic studies (including duration and dose scheduling).
I.A.4 Short-term exposure	CHPPM	Definition (Strategy -Section 1)
	IOM Study Panel /USAMRICD	Contract research panel commissioned to set standard definitions for subchronic studies (including duration and dose scheduling).
I.A.5 Temporary Exposure	CHPPM	Definition - (Strategy Section 1)
	IOM Study Panel (draft)/USAMRICD	Contract research panel commissioned review standard definitions for purposes of acute studies (including duration and dose scheduling).

Table 6. Low-Level Exposures Research Program Areas (Continued)
Ongoing and Planned Projects FY99, Listed by Program Area Identified in DoD Strategy to Address Low-Level Exposures

Program Area	Known work in progress/Funding Agency	Scope of Work
I. IDENTIFICATION: **B. Low-level CWA Hazard Assessment**		
I.B.1 Single event single agent exposures	ECBC (JSIG)	Series of Low-Level Toxicological Studies
	CHPPM	*TG 230 A - individual chemical guideline concentration values for a variety of exposure durations*
	USAMRICD	Organophosphonate Cardiovascular Toxicity in the Open-chested Porcine Model.
	Herman vanHelden, Ph.D. TNO Prins Maurits Lab, Netherlands/MRMC	Low-level Exposure to GB Vapor in Air: Diagnosis/ Dosimetry, Lowest Observable Effect Levels, Performance-Incapacitation, and Possible Delayed Effects
I.B.3 Repeated/chronic/long-term exposures	CHPPM-SECWG	*TG 230B - individual chemical guideline concentration values for a variety of exposure durations – TG230B is for 'long-term*
	UMAB/USAMRICD	Molecular Targets for Organophosphates in the Central Nervous System.
	Texas Tech Univ Health Science Center/USAMRICD	Cellular and Molecular Neuropathophysiology of Subacute Organophosphate Chemical Warfare Agents.
	WRAIR/USAMRICD	Chronic Effects of Chemical Warfare Agent Exposure.
	USAMRICD	Development of an Appropriate Animal Model to Study Effects of Low Dose Chronic CWA Exposure.
	Lovelace Respiratory Research Institute Albuquerque, NM/MRMC	Long-term Effects of Subclinical Exposures to Sarin
I. IDENTIFICATION: **C. Concurrent exposures**		
I.C.1 Toxic environmental substances	CHPPM- SECWG	TG 230 - individual chemical guideline concentration values for a variety of exposure durations
I.C.1a - pesticides	CHPPM-SECWG	TG 230
I.C.1b -insect/vermin control agents		
I.C.1c -toxic industrial compounds (TICs)	CHPPM- SECWG	TG 230 - individual chemical guideline concentration values for a variety of exposure durations
I.C.1c -toxic industrial compounds (TICs)	US Army Medical Research and Materiel Command (USAMRMC)	Gulf War Illnesses Research: Innovative Biologically-Based Toxicology Methods & Models For Assessing Mixed Chemical Exposures With Potential Neuro-Toxicological & Other Health Effects

Table 6. Low-Level Exposures Research Program Areas (Continued)
Ongoing and Planned Projects FY99, Listed by Program Area Identified in DoD Strategy to Address Low-Level Exposures

Program Area	Known work in progress/Funding Agency	Scope of Work
I.C.2 Low grade radiation	CHPPM	*HPD*
I.C.2a nuclear	AFRRI	Effects of low-level radiation exposure on disposition and effect of other battlefield exposures
I.C.2b electromagnetic		
I.C.3 preventive medications	USAMRMC	Gulf War Illnesses Research: Interactions Of Drugs, Biologics And Chemicals In Service Members In Deployment Environments
I.C.4 fuels	--Air Force Institute for Environment, Safety and Occupational Health Risk Analysis (IERA) -- CHPPM	*--Fuels (especially jet fuels) toxicology* *--(OEMD/DOHS/TOX)*
I.C.4a diesel fuel	‘’	‘’
I.C.4b jet fuel	‘’	‘’
I.C.4c other hydrogen-based fuels	‘’	‘’
I.C.5 hazards	CHPPM-HHA	*Program mission*
I.C.5a occupational	CHPPM	TG231-describes field occupational hazards (from chemicals)
I.C.5b battlefield	FM 100-14 ; AFI 91-213; AFPAM 91-215; OPNAV Instruction 3500	Operational Risk Management
	CHPPM- HHA	*program mission*
	USAMRMC	Gulf War Illnesses Research: Integrated Psychosocial & Neuroscience Research On Stress & Somatic Consequences
	Medical Follow-up Agency Institute of Medicine/ National Academy of Sciences/MRMC	Long Term Follow-up of Veterans Experimentally Exposed to Sarin and Other Anticholinesterase Chemical Warfare Agents
	Barry W. Wilson University of California, Davis/MRMC	Low-Level Sarin Neurotoxicity and its Modulation by Pyridostigmine
	M. Abou-Donia, Ph.D. Duke University Medical Center/MRMC	Long-Term Effects of Subchronic Exposure to Sarin, Alone and with Stress or Other Chemicals
	Satu M. Somani, Ph.D. Southern Illinois University/MRMC	Sarin and Pyridostigmine Interaction under Physical Stress: Neurotoxic Effects in Mice
	Carl Olson, Ph.D. Battelle/MRMC	Neurophysiologic and Neuropathologic Effects in Monkeys of Low-Level Exposures to Sarin, Pyridostigmine, Pesticides, and Botulinum Toxoid
	Carl Olson, Ph.D. Battelle /MRMC	Assessment of Subchronic Neurobehavioral and Neuropathologic Effects in Rats

Table 6. Low-Level Exposures Research Program Areas (Continued)
Ongoing and Planned Projects FY99, Listed by Program Area Identified in DoD Strategy to Address Low-Level Exposures

Program Area	Known work in progress/Funding Agency	Scope of Work
II. PROTECTION		
II. A- antidotes & prophylactics	USAMRICD	Modulation of Intracellular Calcium as a Strategy for Protection Against GD-induced Brain Damage.
	USAMRICD	Electrophysiological Analysis of Toxic Effects in Cell Cultures.
II. B - PPE/clothing		
III DECONTAMINATION		
III. Decontamination	JSMG/ECBC	General Agent decontamination
	ECBC	Sorbent Decon
IV. DETECTION*		
IV.A chemical agent		
IV.A.1 alarms/sensors	JSMG	Multiple projects funded/DOD but primary projects lead by ECBC(Army)
IV. A.2 - continuous monitors	JSMG	Multiple projects funded/DOD but primary projects lead by ECBC(Army)
IV.B. Biomarkers for CWA Exposure	USAMRICD	Use of differential display PCR to determine altered gene expression after exposure to HD in cultured human keratinocytes.
	USAMRICD	Improved detection methods for nerve agent exposures from biological samples.
	TNO Prins Maritus Lab / USAMRICD	Improved detection methods for HD metabolites from biological samples.
	ECBC	Biomarkers for CWA Exposure- Differential Display PCR for Determining OP Altered Gene Expression
	JSMG/ECBC	Invitro biomarkers of threat agents
	USAMRICD	Improved detection methods for HD exposure from biological samples.
V. SURVEILLANCE*		
V.A - Exposure information (recording, reporting, coordinating, retaining)	*CHPPM- DESP*	*Program mission - includes establishing methods to collect exposure information (field data, modeling data, use of GIS systems) then recording and report potential and actual exposures - retaining/incorporating information in surveillance database (see below)*
	CHPPM- DOHRS	*Expanding database systems that documents occupational exposures, health information, etc. – system to be eventually to include deployment surveillance and medical info*

Table 6. Low-Level Exposures Research Program Areas (Continued)
Ongoing and Planned Projects FY99, Listed by Program Area Identified in DoD Strategy to Address Low-Level Exposures

Program Area	Known work in progress/Funding Agency	Scope of Work
V.A.1 type (chemical(s)/rad)		*See DESP above (includes identification initiatives such as AFMIC/JHU initiative)*
V.A.2 concentration and duration		*See DESP above(procedures for collecting and modeling) as well as TG 230 for identifying levels of concern*
V.A.3 location		*See DESP above (use of GIS/intelligence information (see AFMIC/JHU)*
V.B - Effects information (documenting reporting, retaining)	*CHPPM- DESP*	
V.B.1 health effects	*CHPPM- DESP*	
	USAMRMC	Gulf War Illnesses Research: Force Health Protection - Deployment Health.
V.B.2 environmental effects	ECBC	Soil chemical/physical properties affecting fate of CWA-class material in well-characterized soils, mobility and potential transport
	ECBC	CWA biodegradation and environmental persistence (half-life) at low levels in soil and water
	ECBC	Effects of water chemistry on persistence of CWA at low-levels in water (including drinking water)
V.B.3 ecological effects	ECBC	Various ecological and environmental evaluations of agents; bioassays for CWA in soil/water; acute and chronic organism assays (5 individuals studies)
VI. RISK MANAGEMENT IMPLEMENTATION		
VI.A. doctrine/policy	OTSG/CHPPM	Project involves incorporating new projects/guidelines (such as TG 230) into doctrine/training
	JESWG/JPMPG/Navy Bureau of Medicine	Joint Service Instruction On Deployment Health Surveillance And Protection
VI.B. risk communication	CHPPM- ERARCP	Risk communication; now expanding to general training for deployment situations

Program Areas: The strategy of this approach may be structured around the five major program areas governing overall protection of personnel continuous risk management implementation: I. Identification; II. Prevention/Protection; III. Detection; IV. Surveillance; and V. Risk Management Implementation (policy/doctrine/training)

SECTION IV: Framework for 5-Year Research Plan

IV.A. Research Plan

IV.A.1. General. This section provides a framework for the establishment of an overarching comprehensive 5-year DoD Research Plan. The DoD Research Plan for Low-Level Exposures will be consistent and integrated with the existing program areas listed in Table 1; *i.e.*, DoD NBC defense commodity areas of contamination avoidance, individual and collective protection, decontamination, and medical defense. The Plan will greatly enhance activity in the hazard identification program area. This will provide the basis for risk management activities occurring in the remaining four program areas. The framework for the Research Plan describes the general criteria under which the plan will be developed. Ultimately, the process described in this Research Plan will direct which specific studies are performed and how they are evaluated and integrated into applicable doctrine and policy during a 5-year period. Initial funding profiles provided in this plan are based on existing program experience and projected process outcomes. Significant deviations in funding requirements may occur as the process proceeds (*e.g.*, expert panels are convened for program refinement) and data are acquired and analyzed.

IV.A.2. Research Focus. The specific research identified in the 5-Year Plan will focus on data gaps associated with the hazard identification and hazard assessment phases, which include toxicological research as well as model and simulation (M&S) development. The general hazards to be addressed by this research include the classical CWAs (G-series, VX, and HD), as well as other exposures that may occur concurrently with chemical agent exposure resulting in a potential interactive effect. The specific process of hazard identification and assessment is broken into three tiers of research effort. *Tier I* involves data development for hazard assessment; *Tier II* involves basic research; and *Tier III* includes program management and data integration. Section IV.B, below, describes these Tiers in more detail.

As defined in Section I, the goal of the DoD strategy will be to provide appropriate protection and detection capabilities for low-level exposures for the general deployed *military* population (*i.e.*, healthy adult 18~~5~~55 years of age). The primary risk of concern at low-level concentrations are those associated with inhalation of agent vapors. Therefore, research will primarily focus on this route of exposure. Specifically, low-level inhalation exposure limits will be derived in a manner consistent with the approach used to establish national guidelines for temporary and short-term exposures to other toxic industrial compounds.

IV.A.3. Data Review and Integration. Once obtained, hazard identification research data will need to be translated into risk assessment and risk management tools to permit incorporation into appropriate doctrine, policy, and operational decisions. For example, US Army Center for Health Promotion and Preventive Medicine (CHPPM) Technical Guide (TG) 230A[41] will establish the process by which the military will assess identified chemical exposure hazards. This guidance can be used in conjunction with existing operational risk management doctrine to assess multiple

[41]U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM), Technical Guide (TG) 230(A); *Short-term Chemical Exposure Guidelines for Deployed Military Personnel*, Draft, May 1999. MCHB-TS-EHR, APG-EA MD.

hazards relative to one another and make appropriate risk management recommendations that may include determining whether there are more significant health risks than those posed by potential chemical exposures.

Since integration of research data is vital to producing meaningful risk assessment, the Research Plan will include a mechanism for periodic review of the research effort. This will include In-Process-Reviews of the individual research tasks to ensure that supported research tasks are designed and executed to generate the data necessary for meaningful hazard assessment. The individual research tasks, the Research Plan, and the progress of the research program also will be subject to periodic external peer review. Specifically, three levels of peer-review are anticipated. First, a select panel of scientists will review the Research Plan itself. Second, all research proposals submitted under the Plan will undergo a two-phase review: an external review for scientific merit, and an internal review for program relevance. Third, an external select panel will again review any integration by this Research Plan. Specifically, this integration will ensure technical/programmatic reviews for course correction as well as integration of information across other program areas requiring such information.

Program areas other than hazard identification (*i.e.*, prevention, decontamination, detection, and surveillance) are also an integral part of the overall strategy, so issues such as instrumentation, equipment development, and medical diagnostics will be described in the Research Plan in terms of information integration. Specifically, the Plan will describe the process in which technical information will be appropriately assessed, reviewed, and then integrated into necessary policy and doctrinal modification as well as into the detection, prevention, and surveillance development program areas. Specific aspects of these program areas that will be evaluated as hazard identification data becomes available are listed in Table 7. The process of data integration will incorporate the use of decision analysis tools, work group collaborations involving key stakeholders, and review processes at various levels including review by non-DoD components.

Table 7: Research Program Areas

PROTECTION
- Protection Equipment
- Medical Intervention

DECONTAMINATION
- Decontaminants (Material and Procedures)
- Dewarning

DETECTION
- Types:
  - Alarms
  - Real-Time Monitors
  - Diagnostic
- Conditions
  - Low-Level (temporary exposure duration)
  - Low-Level (short-term exposure duration)
  - Low-Level (long-term exposure duration)
  - Single chemical agent
  - Multi-agent hazard

SURVEILLANCE
- Data Collection
- Data Evaluation
- Record-Keeping

IV.A.4. Program Coordination and Policy Evaluation. The Office of the Secretary of Defense (OSD) NBC Defense Steering Committee, with the Deputy Assistant to the Secretary of Defense for Chemical and Biological Defense, DATSD(CBD), serving as the Executive Secretary and OSD focal point, provides direct oversight of the DoD Chemical and Biological Defense Program (CBDP). The Joint Service NBC Defense Board, with the Army serving as the Executive Agent for the program, coordinates and integrates research, development, test, and evaluation and acquisition requirements for the DoD CBDP. The DoD CBDP Strategy to address low-level exposures focuses primarily on the hazard identification aspects of CWAs. However, the efforts of other components of the overall program relating, either directly or indirectly, to the issue of low-level exposures will be integrated. Key stakeholders involved in the areas of detection, prevention, and surveillance will be integrated into the hazard identification research process through a mechanism involving the translation of information from the research data into technical references suitable for development of doctrine and policy. For example, specific monitoring and detection development issues are overseen by the Joint Service Materiel Group (JSMG) and related operational application requirement issues addressed by the Joint Service Integration Group (JSIG).

In addition, initiatives of other DoD stakeholders that are not in the chemical and biological defense community also must be integrated into the process to ensure consistent policy and doctrine. Among these include the Army Medical Command NBC-Environmental (NBC-E),

Marine Corps Combat Development Command, the Medical Resources, Plans and Policy for Naval Operations, U.S. Special Operations Command, and the Air Force Office of the Surgeon General. Similarly, DoD directives on joint medical surveillance assign responsibilities for surveillance, hazard assessment, and prevention of environmental threats during deployments to the Assistant Secretary of Defense (ASD) for Health Affairs, the Service Surgeons General, CINC surgeons, and JTF surgeons. Currently, the Joint Environmental Surveillance Working Group (JESWG) under the Joint Preventive Medicine Policy Group (JPMPG) is developing specific instructions and guidelines to implement detection and surveillance for non-CWA environmental threats during deployments.

The Research Plan will be coordinated as practicable with the Research Working Group of the Military and Veterans Health Coordinating Board to ensure minimal duplication of effort and leveraging of departmental resources. The coordinating mechanism for these and other Joint Staff elements and programs will be established in the 5-year Research Plan.

Finally, guidance, doctrine, and policy also must be evaluated in light of potentially applicable non-DoD requirements [*e.g.*, North Atlantic Treaty Organization (NATO)]. The plan will delineate all key DoD and non-DoD elements as well as the necessary mechanisms of coordination. One such mechanism or tool for disseminating either non-DoD guidance (such as NATO) or to integrate new data into new guidelines will be through the USACHPPM TG230A, in which specified concentration guidelines will be the primary basis by which new data will be used to validate/modify the established criteria. Another such mechanism will be through collaborative working groups such as the NATO Preventive Medicine Working Group and the Military and Veteranś Health Coordinating Board established under PRD-5. Other data will be assessed against military specifications or existing policies. Upon resourcing and implementation, this 5-year Research Plan will identify the key stakeholder representatives in each program area and the primary mechanism to ensure proper information transfer.

IV.B. HAZARD IDENTIFICATION

IV.B.1. <u>Approach.</u> This is a process of identifying hazards of concern and establishing what concentrations lead to significant health effects. It is the primary focus of this research plan. Although the hazards of concern are related to human toxicity, ethical considerations require that much of the data will be generated in non-human *in vivo* and *in vitro* models. To provide a meaningful assessment of human hazard, modeling and simulation (M&S) efforts that integrate *in vivo* and *in vitro* research and extrapolate these data to human exposures are crucial. The research must also focus on known or suspected endpoints/effects of concern. One ongoing project that is critical to prioritizing effects of concern and which is specifically recommended is a follow-on study to the National Academy of Sciences (NAS) study on effects of human CWA exposure (Possible Long-Term Effects of Short-Term Exposure to Chemical Agents; NAS, 1984).[42]

[42] National Academy of Sciences -National Research Council; *Possible Long-Term Effects of Short-term exposures to Chemical Agents*; Volumes I-III, 1984.

With respect to exposure to multiple hazards, DoD will review scientific literature and scientific sources, ongoing work by the Research Working Group, and risk assessment methodologies in determining the priority of interactions among multiple chemicals. Two key scientific sources that will be referenced are the NAS, Institute of Medicine Report on the Health Consequences of Service During the Persian Gulf War[43], and the Institute of Medicine (IOM) Report on Interactions of Drugs, Biologics, and Chemicals in U.S. Military Forces, 1996.[44] Specifically, the IOM acknowledges that the scope of potential drug, chemical, and biological interactions to which military personnel may be exposed is quite large. The IOM therefore advocates an approach of categorizing interactions into three classes based on whether there is a (1) known interaction between two or more compounds, (2) potential interaction, or (3) unknown interaction—so that different evaluation strategies may be applied to each class and that actual *in vitro*, animal, and human studies be kept to a manageable level. The IOM concluded in its 1996 report that "the diversity and number of agents precludes not only the testing of all possible combinations for interaction but also the development of systems that could be used to identify and predict with confidence all possible interactions that could result in increased toxicity."[45]

In summary, the research described and proposed herein is designed to yield the most significant and necessary information with regards to hazards associated with CWA. While such research may not provide all answers to all potential hazards, it makes the most of available resources through a prioritization process and the application of modeling and simulation and established a research framework for future additional studies.

As described in Section IV.A.2, this 5-year Research Plan will utilize a three-tiered approach to address the current data gaps:

Tier I is work performed employing community-accepted toxicological procedures to generate data for hazard assessment. It includes two-species animal inhalation studies for temporary and short-term exposures, specifically with the goal of identifying low-level exposure concentrations and the associated biological effects. Existing methodologies and protocols, including Good Laboratory Practices (GLP), will be used in Tier I. In addition, M&S will be used to enhance and expedite the process of data development by reducing the number of parallel experiments required to verify the toxicology of chemically similar agents and by reducing the number of animals needed to establish dose ranges. Also, a specifically identified study will be implemented for each agent on the basis of a selected potential interaction. Potential interactions of concern will be identified through the prioritization of potential interactions identified by IOM, 1996. Potential interactions will be identified on the basis of similar target organs, toxicokinetic patterns, pharmacokinetics, or pharmacodynamics. Prioritization and selection of interaction studies will be based on the probabilities of occurrence of the concurrent exposures (chemical agent and other hazards). This proposed plan and estimated resource requirement projections assume a single interaction of concern will be funded per agent. This unit cost is assumed to

[43] Institute of Medicine, *Health Consequences of Service During the Persian Gulf War, Recommendations for Research and Information Systems*, 1996.
[44] Institute of Medicine, *Report on Interactions of Drugs, Biologics, and Chemicals in U.S. Military Forces*, 1996.
[45] *Ibid*., p.6.

represent a general cost required to perform studies on each additional individual interaction study as well.

Tier II is basic research that may lead to community accepted procedures, and then used to generate data for hazard assessment. It involves the basic research needed to address potential new method development. For example, while Tier I will focus on effects that occur up to 14 days post exposure,[46] Tier II will consider the potential long-term effects. Similarly, while standard endpoints will be evaluated in Tier I, further evaluation and research of new biomarkers may be performed in Tier II. Finally, initial identification of an interaction may need to be further researched. These basic research needs will include new method development as well as M&S applications. As new methods are developed and validated, they will be evaluated and incorporated into Tier I research as deemed necessary.

Tier III includes the overall program management and data integration process. This includes standing technical oversight to ensure that candidate procedures are passed from research efforts to accepted protocols for data generation. Another primary objective of the Strategy is to ensure that all relevant research data are properly assessed and integrated into appropriate guidance, doctrine, and policy. This addresses the fifth program area identified in the Low-Level Strategy, ₱olicy, Procedures, and Review.”This will include proper review and evaluation of both the proposed plan and the individual research proposals. DoD will ensure that a continuous evaluation of the overall program is performed to ensure achievement of the stated Program purpose, scope, and objectives. DoD will also refine research initiatives within the Low-Level Strategy as necessary to maintain programmatic focus. Furthermore, review and assessment of the process and decisions regarding the integration of the hazard identification data into other program areas will be continuous. The review processes, including identification of primary non-DoD entities, will be described in the Plan.

The 5-Year Research Plan requires a detailed evaluation of existing data to determine specific study needs. Specific research approaches and considerations (listed in Table 8) will be used when establishing the specific Research Plan of studies. However, on the basis of a general evaluation of data needs in accordance with the described goal of the Low-Level Research Strategy, this tiered-approach was used to establish initial resource requirements for the 5-year Research Plan (Table 9). The estimate in Table 9 reflects the general magnitude of expected costs over a 5-year period, if this plan were implemented in total. DoD components will evaluate alternatives to satisfy requirements within the DoD resource deliberation process. Current resources are not programmed to implement the entire 5-year Research Plan. Funding and prioritization of studies will be examined, validated, and resourced, as appropriate, with the Departments overall budgetary constraints. Results of future studies will potentially require adjustments to the funding and prioritization of studies as described.

[46] For rationale on duration of study, see page 16.

Table 8. Research Approaches and Considerations for Development of the 5-Year Research Plan.

Identification of low-level concentrations:

- Single low-level CWA
- Single higher level CWA
- Repeated exposures during short-term exposures
- Study duration 14-days post exposure
- Study duration greater than 14-days post exposure

Study Modalities:

- *In vitro* toxicology
- *In vivo* toxicology
- Modeling and Simulation
- Low-dose Extrapolations
- Physiologically Based Pharmacokinetics (PB/PK)/Uptake
- Quantitative Structure Activity Relationships (QSAR)
- Body Region Hazard Analysis (BRHA)

Study Types:

- Toxicokinetics
- Toxicodynamics
- Neurological
- Immunological
- Mutagenicity/Carcinogenicity
- Reproductive/Developmental
- Genomic/Transgenics

Endpoint Selections:

- Clinical signs
- Biochemical
- Behavioral
- Pathological
- Electrophysiological

IV.B.2. Projected Resource Requirement Estimate for Low-Level 5-year Research Plan.

Table 9 outlines the general magnitude of costs over a 5-year period for the DoD Low-Level Research Plan. It provides an estimate of projected funding requirements necessary to achieve the goal set forth in the DoD Low-Level Strategy. It is anticipated that fund distributions between tiers would shift over the 5-year program, with greater initial investments in Tier II shifting to greater investments in Tier I in later years. This resource requirement estimate is based on the goal, scope, and prioritization scheme described in the proposed DoD Low-Level Strategy. In addition, there are certain key assumptions and caveats that underlie the specific funding estimates and timelines indicated.

1) DoD has ongoing initiatives, as indicated in Section III, that are currently resourced and address some aspects of each of the three tiers of the proposed Research Plan. These initiatives are currently funded at approximately $15 million. These initiatives lay a basic infrastructure from which future studies could be built. The studies the plan identifies and these associated projections are intended for continuing and expanding work necessary to address Congressional concerns regarding potential exposures of U.S. forces to low-levels of CWAs and associated hazards anticipated during deployments.

2) The estimated resource requirement for the 5-year Research Plan to provide the data and models to address the low-level effects for three chemical warfare agents (GB, VX, and HD) is *$78 million*. In addition, studies on the interaction between low-level exposure to each of these three chemical warfare agents in combination with only one other compound is *$22 million*. Each additional interaction study between low-level exposure to one chemical warfare agent and one additional compound is estimated would cost approximately $78 million.

3) It should be noted the limited number of laboratories capable of performing the necessary pulmonary-based studies with chemical agents may impact the completion of necessary studies within the 5-year timeframe. Furthermore, adding studies/research (*e.g.*, for other agents and /or endpoints or interactions) would *significantly* add to the projected timelines cited. The resource requirement estimate does *not* address the establishment of new laboratory capabilities since they would be a significant resource expenditure and would be unlikely to contribute more than marginally in the requisite 5-year period.

Table 9. Low-Level 5-year Research Plan Resource Requirement Estimate

(see Section IV.B.2 for explanation)

	G-Agent Series (cost estimates from ongoing GB work)	**VX** (compared with GB and anticipated difficulties in method standardization)	**HD** (compared with GB and anticipated difficulties in method standardization)
TIER I. Data Development for Hazard Assessment	$12M	$15M	$17M
• Method Standardization			
• Study implementation and completion			
• Temporary and short-term (single and repeated exposures) duration studies with 14-day effects observation			
• Biological endpoints (biomarkers) using existing standing protocols and behavioral endpoints			
• Animal inhalation studies (rodent and non-rodent models)			
• Modeling and Simulation			
Specific Interaction Study*	$7M*	$7M*	$8M*
* unit cost for single interaction study (*i.e.*, one chemical warfare agent at one concentration interacting with one other compound)			
Subtotal (Tier I)	**$19M**	**$22M**	**$25M**
TIER II. Basic Research	$7M	$6M	$6M
• New biomarkers, interaction methods, long-term effects, and modeling and simulation development			
Subtotal (Tier I + Tier II)	**$26M**	**$28M**	**$31M**
TIER III. Program Management	**$5M**	**$5M**	**$5M**
• Research prioritization, data integration, quality control, independent peer reviews of project plans, execution and integration, and development of risk assessment tools to support policies, doctrine, and procedures			
TOTAL (Tier I + Tier II + Tier III)	**$31M**	**$33M**	**$36M**

Annex 1: Selected References

Curtis D. Klaassen, editor, *Casarett and Doull's Toxicology: The Basic Science of Poisons* (5th ed.), (McGraw-Hill: New York), 1996.

Field Manual 100-14, *Risk Management*, Headquarters Department of the Army, Washington D.C., 23 April 1998.

House of Representatives Bill HR 4036, Persian Gulf War Veterans Health Act of 1998

Institute of Medicine, *Health Consequences of Service During the Persian Gulf War, Recommendations for Research and Information Systems*, 1996.

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National Science and Technology Council Report, Presidential Review Directive (PRD)5, *Planning for Health Preparedness for and Readjustment of the Military, Veterans, and Their Families after Future Deployments*, August 1998.

Report to Congressional Requesters: *Chemical Weapons – DoD Does Not Have a Strategy to Address Low-Level Exposures*; United States Government Accounting Office (GAO/NSIAD 98-228), September 1998.

Strom Thurmond National Defense Authorization Act for Fiscal Year 1999, Authorization Conference Language, H. Report 105-736,Section 247: Chemical Warfare Defense; 1998.

U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM), Technical Guide (TG) 230(A); *Short-term Chemical Exposure Guidelines for Deployed Military Personnel*; draft August 1998. MCHB-TS-EHR, APG-EA MD.

Annex 2: Congressional Language

Strom Thurmond National Defense Authorization Act for Fiscal Year 1999, Authorization Conference Report, H. Rpt. 105-736, Sec. 247: Chemical Warfare Defense (*Public Law 105-261*, 17 October 1998), p. 39; and Authorization Conference Report, H. Rpt. 105-736, Report Language, p. 591.

P.L. 105-261, Section 247

SEC. 247 CHEMICAL WARFARE DEFENSE:

(a) Review and Modification of Policies and Doctrines: The Secretary of Defense shall review the policies and doctrines of the Department of Defense on chemical warfare defense and modify the policies and doctrine as appropriate to achieve the objectives set forth in subsection (b).

(b) Objectives: The objectives for the modification of policies and doctrines of the Department of Defense on chemical warfare defense are as follows:

(1) To provide for adequate protection of personnel from any exposure to a chemical warfare agent (including chronic and low-level exposure to a chemical warfare agent) that would endanger the health of exposed personnel because of the deleterious effects of-

(A) a single exposure to the agent;

(B) exposure to the agent concurrently with other dangerous exposures, such as exposures to--

(i) other potentially toxic substances in the environment, including pesticides, other insect and vermin control agents, and environmental pollutants;

(ii) low-grade nuclear and electromagnetic radiation present in the environment;

(iii) preventive medications (that are dangerous when taken concurrently with other dangerous exposures referred to in this paragraph);

(iv) diesel fuel, jet fuel, and other hydro-carbon based fuels; and

(v) occupational hazards, including battlefield hazards; and

(C) repeated exposures to the agent, or some combination of one or more exposures to the agent and other dangerous exposures referred to in subparagraph (B), over time.

(2) To provide for--

(A) the prevention of and protection against, and the detection (including confirmation) of, exposures to a chemical warfare agent (whether intentional or inadvertent) at levels that, even if not sufficient to endanger health immediately, are greater than the level that is recognized under Department of Defense policies as being the maximum safe level of exposure to that agent for the general population; and

(B) the recording, reporting, coordinating, and retaining of information on possible exposures described in subparagraph (A), including the monitoring of the health effects of exposures on humans and animals, environmental effects, and ecological effects, and the documenting and reporting of those effects specifically by location.

(3) To provide solutions for the concerns and mission requirements that are specifically applicable for one or more of the Armed Forces in a protracted conflict when exposures to chemical agents could be complex, dynamic, and occurring over an extended period.

(c) Research Program: The Secretary of Defense shall develop and carry out a plan to establish a research program for determining the effects of exposures to chemical warfare agents of the type described in subsection (b). The research shall be designed to yield results that can guide the Secretary in the evolution of policy and doctrine on exposures to chemical warfare agents and to develop new risk assessment methods and instruments with respect to such exposures. The plan shall state the objectives and scope of the program and include a 5-year funding plan.

(d) Report: Not later than May 1, 1999, the Secretary of Defense shall submit to the Committee on Armed Services of the Senate and the Committee on National Security of the House of Representatives a report on the results of the review under subsection (a) and on the research program developed under subsection (c). The report shall include the following:

(1) Each modification of chemical warfare defense policy and doctrine resulting from the review.

(2) Any recommended legislation regarding chemical warfare defense.

(3) The plan for the research program.

REPORT LANGUAGE

Chemical Warfare Defense (Sec. 247)

The House bill contained a provision (Sec. 723) that would authorize the Secretary of the Air Force to conduct research on health-related environmental and ecological effects of exposure to chemical, biological and radiological hazards and to develop more accurate risk assessment tools. In addition, the provision would authorize an increase of $1.8 million in the Defense Health Program to conduct this risk assessment program.

The Senate amendment contained a provision (Sec. 1045) that would direct the Secretary of Defense to review, and modify as appropriate, Department of Defense chemical warfare defense policy and doctrine regarding the protection of U.S. forces against exposure to low-levels of chemical warfare agents. In addition, the provision would require the Secretary of Defense to report to the congressional defense committees on any modification to chemical warfare policy and doctrine as a result of the review, and establish a plan for a five-year research program to assist the Secretary in developing policy and doctrine on exposure to low-level chemical agents.

The conferees agree to a provision that would direct the Secretary of Defense to review and modify Department of Defense chemical warfare policy and doctrine to ensure that U.S. forces are adequately protected against any exposure to chemical warfare agents, to include exposure to low-levels of chemical agents and other potentially toxic substances in the environment that would endanger the health of exposed personnel. Additional areas to be included in the review are the exposure of U.S. forces to low-grade nuclear and electromagnetic radiation, preventive medications, and diesel, jet, and other hydro-carbon based fuels.

The provision would also require the Secretary of Defense to develop and carry out a plan to establish a research program that would assist the Secretary in developing policy and doctrine, as well as new risk assessment methods and instruments, with respect to the effects of exposure to chemical warfare agents and other toxic substances, in order to ensure that U.S. forces are adequately protected against exposure to chemical warfare agents and toxic substances. The provision also requires that a five-year budget plan be developed. The Secretary of Defense is required to report to the congressional defense committees not later than May 1, 1999, on the review of DoD policies and doctrine on exposure to chemical warfare agents and toxic substances, and any recommendations to modify current policy and doctrine as a result of the review, any recommended legislative provisions, and the plan to establish the research program.

Annex 3: Acronyms and Abbreviations

AFMIC – Armed Forces Military Intelligence Center
CAM – Chemical Agent Monitor
CBDP – Chemical and Biological Defense Program
CHPPM – U.S. Army Center for Health Promotion and Preventive Medicine
CWAs – Chemical warfare agents
DESP – Deployment Environmental Surveillance Program
DoD – Department of Defense
ECBC – Edgewood Chemical and Biological Center
EHRARCP – Environmental Health and Risk Communication Program
ERPG – Emergency Response Planning Guideline
FM – Field Manual
GPL – General Population Limit
HHA – Health Hazards Assessment Program
HPD – Health Physics Division
IDLH – Immediate Danger to Life and Health
IOM – Institute of Medicine
JESWG – Joint Environmental Surveillance Working Group
JHU – Johns Hopkins University
JPMPG – Joint Preventive Medicine Policy Group
JSIG – Joint Service Integration Group
JSMG – Joint Service Materiel Group
M&S – Modeling and simulation
MOPP – Mission-Oriented Protective Posture
MRICD – U.S. Army Military Research Institute of Chemical Defense
MRIID – U.S. Army Military Research Institute of Infectious Diseases
MRMC – U.S. Army Medical Research and Materiel Command
NIOSH – National Institute of Industrial Safety and Health
OSD – Office of the Secretary of Defense
OTSG – Office of the Surgeon General
PRD – Presidential Review Directive
SBCCOM – U.S. Army Soldier Biological and Chemical Command
SECWG – Soldier Exposure Criteria Working Group