APPENDIX D

Strategy for Research on the Health Effects of Exposure to Low-Levels of Organophosphorous Chemical Warfare Nerve Agents

EFFECTS OF LOW-LEVEL EXPOSURE TO CHEMICAL WARFARE AGENTS

A RESEARCH STRATEGY

Research Working Group
Persian Gulf Veterans Coordinating Board

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INTRODUCTION

Background

Confirmed evidence regarding use of chemical/biological warfare agents during the Persian Gulf War has not been established to date. Both the Defense Science Board (DSB) in its final report (DSB, 1994) and the Institute of Medicine's (IOM) Panel on the Health Consequences of Service during the Persian Gulf War (IOM, 1995) in its interim report (IOM, 1995) concluded that reports of the possible use of CBW agents could not be confirmed and that bombing of Iraqi munitions storage areas did not cause CBW agent exposure of service personnel. While awaiting assessment of the DSB, the National Institutes of Health (NIH) panel drew no conclusions about the presence or absence of CBW (NIH, 1994). The IOM panel in its interim report (IOM, 1995) stated that claims of exposure to chemical or biological warfare agents should not be made or given credence in the absence of reliable substantiating data. Despite this, the DoD established the Persian Gulf Investigations Team (PGIT) in 1995 to investigate, among other things, reports of possible CBW exposure provided to a 1-800 hotline. Furthermore, many of the ongoing epidemiological investigations of Persian Gulf veterans' illnesses collect self-reports of veterans on chemical agent exposure. Although these data may have value in assessing risk factors, the potential for report bias is a persistent problem. These research efforts also encompass other neurotoxic risk factors such as organophosphate pesticides and the carbamate pyridostigmine bromide (PB). However, in the past there has been no major, organized research effort focused specifically on the health effects of exposure to low-levels of chemical warfare agents.

In June 1996, DoD announced that a munitions bunker (#73) in Khamisiyah, Iraq, destroyed by U.S. demolition teams on March 4, 1991, reportedly contained the chemical agents sarin and cyclosarin. In addition, in testimony before the Presidential Advisory Committee meeting on March 18, 1997 (PAC, 1997), the CIA indicated that a pit containing rockets which contained sarin was also destroyed by US troops on March 10, 1991. Because of these demolitions, it is possible that some U.S. military personnel in the vicinity were exposed to low levels of chemical warfare agents. However, quantitatively measured exposure data do not exist. In addition to the events at Khamisiyah, chemical weapons storage sites at Muhammadiyat, and Al Muthanna, Iraq (northwest of Baghdad), were destroyed by Allied bombing at the beginning of the Persian Gulf War, creating a potential risk of chemical agent exposure downwind of these sites.

Testimony provided to the Presidential Advisory Committee meeting on July 8-9, 1996 (PAC, 1996a) by representatives of the United Nations Commission charged with the accounting and destruction of weapons of mass destruction in Iraq, and by the US Central Intelligence Agency (CIA), suggest that Khamisiyah was the only site in southern Iraq and Kuwait at which chemical weapons were present. If this is so, the incident at Khamisiyah may be isolated. There could be other "unknown" sites containing chemical weapons since Iraqi chemical weapons were either not marked or inconsistently marked for identification and could have been inadvertently destroyed along with other

conventional munitions. As a result there now exists a sufficient degree of uncertainty regarding potential exposures to chemical warfare agents that it has become a valid subject of research.

Two exposure issues immediately arise. The first one relates to the potential exposure of troops present at the Khamisiyah site at the time of demolition, and the potential exposure of troops as a result of the bombing of the Muhammadiyat and Al Muthanna weapons depots, and unknown chemical sites identified at this time as "conventional". The second relates to the more general issue of chemical agent exposure.

In testimony at the July 8-9, 1996 PAC meeting (PAC, 1996c), contractors to the Central Intelligence Agency (CIA) presented the results of model calculations predicting ground level concentration of chemical agent as a function of distance and direction away from the March 4 detonation site at Khamisiyah (CIA, 1996). The model predicts that at the location of the troops chemical agent concentration should have been at levels below which even acute mild effects would be predicted, given current knowledge about the effects of these agents. The CIA also modeled the plumes resulting from the bombings at Muhammadiyat and Al Muthanna. The model also predicts low exposure levels for troops located 400 - 500 km south of the sites. In July, 1997 DoD's Office of the Special Assistant for Gulf War Illnesses (OSAGWI) and CIA issued the results of modeling of exposure from the pit demolition of March 10, 1991. Although this model predicts that nearly 100,000 troops may have been exposed to some level of sarin, it suggests that no troops were exposed to levels at levels required to cause acute effects (OSAGWI, 1997a). At the moment, model predictions provide some reassurance. However, the definitive conclusions about health effects cannot be made from such models alone, particularly in regard to mild, chronic residual subclinical effects of exposure[1].

Among troops in the vicinity of Khamisiyah at the time of the detonations, there have been no reports to date of acute illnesses or symptoms known to be associated with exposure to nerve agents. Conventional understanding of the mechanisms of toxicity of nerve agents has suggested a very low likelihood of chronic effects from a short duration, subclinical exposure (one which does not produce acute symptoms but may have a biological effect such as, in the case of sarin, a small reduction of serum cholinesterase). However, the amount of data to quantitatively support this assertion is minimal. Appendix A contains a summary of several recent comprehensive reviews (Marrs et al, 1996; Perrotta, 1996; Elson, 1996; Sidell and Hurst, 1997) of the health effects of nerve

[1] A comprehensive description of the events associated with the demolition activities at Khamisiyah can be found in a report by the Investigation and Analysis Directorate (IAD), OSAGWI (OSAGWI, 1997b). The report is posted on the World-Wide Web at http://www.dtic.mil:80/gulflink/khamisiyah/kham7.html. Information on the intelligence history of chemical weapons at Khamisiyah dating back to 1976 is in a report by the CIA Persian Gulf War Illnesses Task Force (CIA, 1997). This report is posted on the World-Wide Web at http://www.dtic.mil:80/gulflink/cia_wp.

agents to help orient the reader to the current scientific issues. The lack of data on the long-term effects of acute subclinical exposures to sarin is the primary reason for developing the current strategy.

Research Response to Khamisiyah

Immediately following the June, 1996, announcement by DoD that U.S. troops blew up a weapons bunker containing chemical warfare nerve agents, the Research Working Group (RWG) began updating the research agenda on Persian Gulf veterans illnesses in light of this new information. Up to this point in time, the research agenda had been largely guided by the assumption that chemical warfare agents were not used by the Iraqis in the Persian Gulf theater of operations, and thus service members were not exposed. Despite this assumption the federal government research portfolio already contained significant research investments in areas relevant to chemical warfare agents (in particular, neurological research relevant to potential nerve agent exposure) (PGVCB 1996, 1997). Nonetheless, a more directed, highly prioritized effort was discussed by the Research Working Group.

The RWG adopted a two pronged approach to reorienting the research agenda in accordance with new information. This approach involved an immediate, short-term response and a more forward-looking long-term response.

New Research Projects on Chemical Weapons Health Effects - Short-Term Response

The short-term response involved immediately funding three new research projects, valued at $2.5 million, on chemical weapons health effects. These projects had already been reviewed by the American Institute of Biological Sciences as a part of another DoD effort and had been found to be scientifically meritorious. These projects are listed below.

- **Diagnosis and Dosimetry of Exposure to Sulfur Mustard** This research will enable retrospective determinations of exposure dose to sulfur mustards at short and long-term intervals after exposure.

- **Toxicokinetics of *O*-Ethyl-*S*-(2-Dissopropylaminoethyl) Methylphosphonothioate in Rats, Hairless Guinea Pigs and Marmosets** This research will provide data on the toxicokinetics and metabolism of the nerve agent VX. This will help in extrapolating animal toxicity data to humans and will provide a basis for optimizing chemical casualty therapy.

- **Transgenic Engineering of Cholinesterase: Tools for Exploring Cholinergic Responses** The project provides animal models with predefined sensitivities to cholinesterase inhibitors which can be used to study the possibility of sensitive subpopulations and the means to identify them.

New Research Projects on Chemical Weapons Health Effects - Long-Term Response

The long-term response to the events at Khamisiyah that has been developed involves soliciting new research projects in the following areas:

- Feasibility of epidemiological studies, including assessment of appropriate design and methodological considerations to assess the possible health effects of sub-clinical, low-level exposures to chemical weapons agents;

- Feasibility of conducting specific epidemiologic research on the health status of personnel determined to be in the vicinity of the Khamisiyah weapons storage area at the time it was destroyed.

- Additional applied toxicological or clinical studies designed to assess the pathophysiological effects of low-level, including subclinical, exposure to chemical warfare agents.

This recommendation to solicit new research on chemical warfare agents, along with other recommendations contained in the 1996 update of the *Working Plan* for research (PGVCB, 1996), led to the release of three DoD Broad Agency Announcements (BAA) for new research, the last one being issued on January 29, 1997. The first BAA was for a study of the feasibility of epidemiological investigations of human subjects thought to be near Khamisiyah, Iraq during the first two weeks of March, 1991. In addition, it requested proposals for animal studies designed to assess the possible long-term or delayed clinical effects of low-level or subclinical exposures to chemical warfare agents. The second BAA was for research on the causal relationships between illnesses among Persian Gulf veterans and a variety of exposures including chemical warfare agents, other hazardous materials, vaccinations, and stress. Based on scientific peer review by the American Institute of Biological Sciences (AIBS) and the programmatic review by the RWG, 12 new research projects from the first two BAA rounds were awarded at the end if FY'97. These projects encompass a number of different possible exposures including sarin, PB, stress, and insecticides alone and in a variety of combinations. Toxicological, clinical, and epidemiologic investigations are included. However, no proposal for a feasibility study for epidemiological investigations centering on the events at Khamisiyah was submitted. The third BAA was for investigations of the role of cognitive, emotional, and physical factors in producing chronic, non-specific symptoms and physiological outcomes. Awards from this latter round are expected to be made in early fiscal year 1998. These new projects, and their areas of investigation, will have an impact on the directions dictated by the strategy to be presented here.

In addition to the above responses, the VA, in conjunction with the RWG, sponsored a *Symposium on the Health Effects of Low-Level Chemical Warfare Nerve Agent Exposure* held March 7-8, 1997 in Cincinnati, OH, in conjunction with the Annual Society of Toxicology meeting. This symposium brought together internationally recognized experts in the chemical, biochemical, toxicological, and clinical effects of chemical warfare organophosphate nerve agents to discuss the current state of knowledge and to help plot a future research course. It is expected that a summary of the *Symposium* will be published in the scientific journal *Fundamental and Applied Toxicology* in early 1998 .

What follows is a strategic approach to resolving some of the uncertainties associated with low-level exposures to nerve agents and their potential for long-term health consequences.

STRATEGY

Purpose

This document presents a strategic approach to research on chemical warfare nerve agents that provides a framework for the organization, direction, and coordination of research on the long-term health effects from single and multiple organophosphate exposures to chemical warfare agents at doses ranging from the toxic, but non-lethal, down to the acute "no observable effects level"(NOEL). The framework encompasses the full spectrum of research from basic toxicology to epidemiology, and is guided by accepted principles and paradigms for risk assessment.

Scope

There is a significant amount of scientific literature upon which is based our current understanding of the acute human health effects from clinical exposures (i.e. exposures that produce acute signs and symptoms in humans) to nerve agents. Such effects may include salivation, miosis, and tachydardia; muscle fasciculation, shortness of breath, seizures, coma and death. There is a high degree of certainty about these acute effects and the exposure doses required to achieve them because of the relative ease with which they can be documented in humans and animals. The present research strategy is not concerned with these well documented effects except to the extent that they may be predictive of long-term chronic residual effects. The present strategy will elucidate the potential long-term health effects of acute and subacute exposures to low-levels of organophosphorous nerve agents.

Definitions

For the purpose of this strategy "low-level" exposure is defined as:

> an exposure that results in minimal reduction in acetylcholinesterase with no or minimal observable clinical signs and, in the case of humans, subjective symptoms. For the purposes of dose-response studies, the following gradation of **low-level** exposures is made:
>
> - *Level 1:* An exposure that results in no clinical signs (and for humans no subjective symptoms), and minimal AChE inhibition (0-20% reduction in red blood cell AChE).
>
> - *Level 2:* An exposure that results in no clinical signs (and for humans no subjective symptoms), and moderate AChE inhibition (>20% reduction in rbc AChE).
>
> - *Level 3:* An exposure that results in mild clinical signs, such as: salivation, miosis, and tachycardia. In humans such an exposure would also be expected to cause symptoms such as shortness of breath.

Because tolerance to the immediate clinical effects of organophosphorous nerve agent exposure can occur with repeated exposures or exposures of at least 24 hour duration, it is assumed that the above low-level exposure definitions refer to the effects observed in single exposures of less than 24 hour duration.

Exposure durations and patterns of interest include:

- Single dose exposures

- Repeated dose exposures:
  At least one (1) day between doses
  Cumulative period of dosing no greater than four (4) weeks
  A minimum of 8 doses and a maximum of 14

- Nerve agent exposure combined with other neurotoxic agents (such as insecticides), exposure to stressors, and other exposures that could interact with nerve agents

Goals

- Increased knowledge and understanding of the long-term effects of low-level exposures to organophosphorous chemical warfare nerve agents;

- Increased knowledge and understanding of the toxicology of interactions of nerve agents with other environmental factors such as insecticides, pyridostigmine bromide, heat, and psychological stress;

- A comprehensive assessment of the possibility of a causal link between low-level exposure to nerve agents and long-term health effects;

- Identification of potential future health problems of veterans exposed to nerve agents;

- Ability to identify troops at potential high risk for low-level nerve agent exposures.

Objectives

1. A central, interagency management of strategy implementation;

2. A complete and independent assessment of the current state of knowledge on low-level chemical agent effects;

3. An evaluation of the federal government research portfolio on relevant research on nerve agent health effects;

4. Identification of research needs (human, animal, in-vitro) and priorities including:
    - Modern/advanced technologies for determination of absorbed and delivered doses;
    - Exploration of the development of practical, validated exposure biomarkers to support retrospective quantitative determination of exposure;
    - Investigations into factors that may place some individuals at higher risk to the health effects of low-level nerve agent exposure.

5. Identification of opportunities for human studies of past exposures including:
    - Previous controlled human studies;
    - Accidental exposures - with and without clinical effects;
    - Scientists and laboratory technicians working with nerve agents;
    - Terrorist uses (e.g., Tokyo and Matsumoto, Japan).

6. New research that will fill information gaps using sound research study designs;
    - ♦ Use of appropriate animal models;
    - ♦ Application of good laboratory practice (GLP) standards;
    - ♦ Use of positive controls;

7. Incorporation of this strategy into the larger context of research required to prepare for future deployments and peace-keeping activities.

Strategies and Initiatives

Objective 1:

- Establish an interagency coordinating group for low-level nerve agent health effects research (tentatively called the Nerve Agent Health Effects Working Group or NAHEWG) that reports to the RWG of the Persian Gulf Veterans Coordinating Board or a research working group established to coordinate research to prepare for future deployments. Membership should consist of research managers and scientists from VA, DoD, HHS, and other agencies with specific expertise relevant to nerve agent health effects;

Objective 2:

- The NAHEWG will identify and commission an independent study group (such as the National Research Council) to conduct a thorough evaluation of the current state of the science on the human health effects of acute exposure to nerve agents, including low-level exposure;

Objective 3:

- The NAHEWG will enjoin each of the member agencies to report to the NAHEWG on their respective agency's relevant research efforts on the health effects of low-level exposure to nerve agents and related compounds;

Objective 4:

- The NAHEWG will evaluate the federal research portfolio of ongoing research in conjunction with the independent assessment of the current state of science.
- The NAHEWG will identify gaps in knowledge about low-level nerve agent health effects with particular emphasis on dosimetry and biomarkers, and will develop a list of research needs;

Objective 5:

- The NAHEWG will work with agencies to identify populations that may be targets of opportunity for human research (clinical and epidemiological). Identification will include any observations derived from the independent research assessment and the federal portfolio review.
- As necessary and using appropriate governmental and non-governmental intermediaries, the NAHEWG shall engage other countries who have data and information sources on the health consequences of accidental and intentional exposures to chemical warfare nerve agents.

Objective 6:

- The NAHEWG will work with participating agencies to generate new research. Such mechanisms would include Requests for Applications (RFA) and Broad Agency Announcements (BAA);
- The NAHEWG will work with participating agencies to develop the language of specific requests for new research consistent with the research needs identified under *Objective 4*.

Objective 7:

- The Research Working Group formed to respond to Presidential Review Directive/NSTC-5 should incorporate this strategic plan into its larger strategic plan for research on health issues related to future deployments and peace-keeping initiatives.

APPENDIX A - Current Understanding of the Human Health Effects of Nerve Agents

History

Nerve agents were first synthesized in Germany prior to World War II. Although Germany had weaponized nerve agents during World War II, they were not used. The Allies found these munitions during the waning stages of that war and began intensive studies on their physical and chemical properties, and on their biological effects. During the following 15 to 20 years, over 100 reports were generated on the effects of low doses of these agents in humans. These reports are the basis for much of our understanding of human health effects of nerve agents. This summary is based on a number of other, more comprehensive, summaries of nerve agent health effects that have recently been written (Marrs et al, 1996; Perrotta, 1996; Elson, 1996; Sidel and Hurst, 1997).

The known nerve agents are tabun (GA), sarin (GB), soman (GD), GF, and VX. One of the properties of these agents that distinguishes among them is their vapor pressure. The G-agents are more volatile than VX, and thus the major route of exposure is from inhalation of their vapors. However, they can also penetrate the skin to cause effects. Because of its low volatility, VX is seldom a vapor threat, but is a greater threat from absorption through the skin when directly applied.

Biochemistry

Nerve agents currently in existence are organophosphorous compounds that inhibit acetylcholinesterase (AChE) in the body. Acetylcholinesterase is an enzyme that keeps the levels of the essential neurotransmitter, acetylcholine, in check. When AChE is inhibited, excess acetylcholine accumulates at cholinergic receptor sites, resulting in potentially dangerous increases in nerve transmission.

Effects

Acute

The acute effects from exposure to a relatively low concentration of vapor are usually at the site of physical contact and not systemic. For example, direct contact with the vapor by the eyes causes miosis, redness of the conjunctiva, dim vision, and pain. Inhalation leads to contact with the respiratory tract, causing rhinorrhea, bronchorrhea, and bronchoconstriction. Exposure by inhalation to a high concentration of vapor leads to systemic effects including seizures, cessation of respiration and cardiac activity, loss of consciousness, and death. Because nerve agents in the vapor form have immediate access to the respiratory tract and systemic circulation, the onset of effects by inhalation takes from seconds to one or two minutes following the onset of exposure.

A small droplet of liquid nerve agent (such as VX) can cause local effects, such as muscle fasciculations and sweating at the site of contact. A slightly larger droplet will also produce systemic effects such as vomiting and diarrhea. A lethal-sized droplet (10 mg for VX) will produce seizures, loss of consciousness, cessation of respiration and

cardiac activity, and death. Except for the lethal-sized droplet, which may cause effects within minutes, the time to onset of effects may be as long as 18 hours after contact. The delay is due to the barrier function of the skin.

The effects of nerve agent are clearly dose-dependent. To quantitatively describe nerve agent effects, it is important to define an adequate dose metric. An *absorbed* dose metric referring to the amount of agent available in the systemic circulation or at receptor sites is ideal. However, with respect to systemic effects, absorbed dose is a complex function of the physico-chemical properties of nerve agent, and the physiological and biophysical properties of the portal-of-entry. For example, not all nerve agent inhaled in a single breath is taken up by the systemic circulation. Some will be exhaled. The actual uptake of a nerve agent into the systemic circulation through inhalation is a function of a number of factors including tidal volume, and inspiratory and expiratory flow rates. For these reasons, a simplified surrogate is used for absorbed dose. This surrogate is known as *exposed* dose, defined as the product of exposure concentration (C in mg/m^3) and exposure time (t in min), or Ct. The utility of Ct as a metric is determined by its ability predict effects for the same value of Ct over different combinations of C and T. For sarin, the most thoroughly studied of the nerve agents, physiological response is proportional to Ct over a wide range of C and T (Haber's Law). The Ct needed to produce mild effects (miosis or rhinorrhea) in humans is about 2-3 $mg\text{-}min/m^3$. In a study referenced in the work of Marrs et al (1996), this held true when C was about 0.08 mg/m^3 and t was 40 minutes or when C was 2 mg/m^3 and t was 1 minute. However, when t becomes greater than approximately 200 minutes, the concentrations of sarin necessary to give a Ct equal to that at 20 minutes lead to fewer or less intense signs and symptoms because the longer exposure time allows some detoxification of sarin. Therefore, when exposures extend over hours, the Ct necessary to produce mild effects is probably larger than the often cited 2-3 $mg\text{-}min/m^3$. Most human studies with sarin have been performed at Ct between 1 and 15 $mg\text{-}min/m^3$. With this dose metric, a synthesis of a variety of experimental studies can be constructed and is outlined below.

The first study of the acute effects of nerve agent in humans was a dose-response study of tabun with Ct = 0.7 - 21 $mg\text{-}min/m^3$. The results define the currently known effects of these agents, namely eye, nose, and airway signs and symptoms. Most of the acute symptoms produced in study subjects, including nausea and vomiting, were relieved by topical application of atropine (an anticholinergic that blocks cholinergic receptors) in the eye. Later studies examined the effects of nerve agent on field performance by soldiers.

In a series of human performance studies, subjects receiving sarin had slight impairment on some tasks, such as a hand-eye task, but not others. Generally, performance was slightly impaired at higher Ct (about 15 $mg\text{-}min/m^3$), but not at lower Ct. Cognitive function and manual dexterity were also slightly decreased.

Physical performance at Ct under 15 mg/m^3 has not been observed to be notably impaired. Pulmonary function after inhalation of small amounts of sarin was unchanged in some studies and slightly impaired in other studies. Military effectiveness was

impaired, particularly at night, but the operations were conducted satisfactorily. Many studies on the eye have concluded that the dim vision noted by subjects is the result not only of the small pupil but also of disturbances in the central visual pathways. Blurred vision occurred only after a high Ct dose.

After application of VX to the skin, subjects had dose-dependent psychological effects, such as psychomotor depression, intellectual impairment, and anxiety. These effects were characterized by difficulty in sustaining attention and a slowing of intellectual and motor processes, but there were no disturbances in language and thinking. These effects could be seen in the absence of physical effects.

Reported accidental exposures are described in Marrs et al (1996). Most of the effects from these exposures were mild, but four individual exposures were severe enough to require mechanical ventilation of the victims. In all cases, the exposed individuals recovered and were able to resume working. One accidentally exposed individual underwent psychological testing. The tests demonstrated administered showed clinical abnormalities shortly after the exposure, but scores returned to normal within several months.

Long-Term Effects

The last three enclosures review the reported long-term effects of these agents in humans and in animals. None of the reviews reports any evidence for carcinogenicity, mutagenicity, or teratogenicity of nerve agents.

The Organophosphate-Induced-Delayed Neuropathy Syndrome (OPIDN) has been reported in humans approximately two weeks after exposure to certain OP insecticides. OPIDN is thought to be caused by inhibition of neurotoxic target esterase (NTE) resulting in axonal degeneration and nerve demyelination. The toxicodynamics of AChE inhibition leading to the acute effects of nerve agent are different than that of NTE inhibition leading to different dose-response characteristics. The dose-response characteristics for OP insecticides to produce OPIDN are such that the acute inhibition of AChE is not sufficient to produce acutely lethal effects. However, nerve agents have different relative dose-response characteristics for AChE versus NTE inhibition. By the time the concentration of a nerve agent such as sarin reaches a level to sufficiently inhibit NTE in an animal to produce OPIDN, it is as much as 60 times the LD_{50} arising from AChE inhibition. Thus, when exposed to a nerve agent alone, production of OPIDN is not possible. However, the experiments to determine the dose of nerve agent to produce OPIDN in animals were done by inhibiting acute effects with atropine and an AChE reactivator. Consequently, nerve agent in combination with agents designed to minimize the effects of AChE inhibition could lead to different conclusions.

The Intermediate Syndrome has not been noted in humans or animals after nerve agent exposure. A recent study using single fiber electromyography found small changes in humans after exposure to small Ct of sarin. These changes reversed and were regarded as having no clinical significance.

Psychological changes as detected with various testing procedures have been noted after a year or two in people exposed to pesticides. Some of these studies were flawed by the lack of matched controls or for other reasons, but some appear valid. Formal studies of long-term psychological changes have not been done in people exposed to nerve agents, either those exposed accidentally or deliberately in experimentally controlled exposures.

OP compounds, both insecticides and nerve agents, have been shown to produce short term changes in the electroencephalogram (EEG). In monkeys, some EEG changes were noted a year later in animals receiving a single high dose or multiple low doses. In a companion study, slight EEG changes were seen in a group of workers a year or more after exposure when the group average was compared to the average of a group of matched controls. Individual EEG's could not be distinguished. No psychological or behavioral studies were done in these groups.

Summary

Although many studies have been done to elucidate the acute clinical effects of nerve agents, there is a paucity of studies on the long-term effects of these agents. A major reason for this is that people exposed to nerve agents, either accidentally or deliberately, had no apparent complaints in the months after the exposure to suggest the need for such studies.

Since it is unlikely that humans will ever again be deliberately exposed to these agents, any new human data on long-term effects will have to come from study of those people exposed years ago, or of those exposed to nerve agents accidentally. Detailed toxicology studies on the long-term effects of low-level exposures will, by necessity, employ animal models and be appropriately designed to facilitate animal-human extrapolations.

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