UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

OAKLAND DIVISION

VIETNAM VETERANS OF AMERICA, a Non-Profit Corporation; SWORDS TO PLOWSHARES: VETERANS RIGHTS ORGANIZATION, a California Non-Profit Corporation; BRUCE PRICE; FRANKLIN D. ROCHELLE; LARRY MEIROW; ERIC P. MUTH; WRAY C. FORREST; DAVID C. DUFRANE; TIM MICHAEL JOSEPHS; and WILLIAM BLAZINSKI, individually, on behalf of themselves and all others similarly situated,

Plaintiffs,

v.

CENTRAL INTELLIGENCE AGENCY; DAVID H. PETRAEUS, Director of the Central Intelligence Agency; UNITED STATES DEPARTMENT OF DEFENSE; LEON PANETTA, Secretary of Defense; UNITED STATES DEPARTMENT OF THE ARMY; JOHN MCHUGH, United States Secretary of the Army; UNITED STATES DEPARTMENT OF VETERANS AFFAIRS; and ERIC K. SHINSEKI, UNITED STATES SECRETARY OF VETERANS AFFAIRS,

Defendants.

Case No. CV 09-0037-CW

EXPERT REPORT OF STEVEN B. BIRD, M.D.

I. INTRODUCTION

A. Retention

1. I have been retained by Morrison & Foerster LLP on behalf its clients, plaintiffs in this matter, Vietnam Veterans Of America, Swords To Plowshares: Veterans Rights Organization, Bruce Price, Franklin D. Rochelle, Larry Meirow, Eric P. Muth, David C. Dufrane, Wray C. Forrest, Tim Michael Josephs, and William Blazinski (collectively "Plaintiffs") to serve as a consultant and expert witness in the above captioned action.

2. I expect to testify at trial regarding the matters discussed in this expert report, and in any supplemental reports or declarations that I may prepare for this matter. I may also testify at trial regarding matters related to my opinions addressed by any expert or fact witness testifying on behalf of Plaintiffs or Defendants Central Intelligence Agency; David H. Petraeus, Director of the Central Intelligence Agency; United States Department of Defense; Leon Panetta, Secretary Of Defense; United States Department of the Army; John McHugh, United States Secretary of the Army; United States Department of Veterans Affairs; and Eric K. Shinseki, United States Secretary of Veterans Affairs (collectively "Defendants"), including but not limited to any reports, testimony, exhibits, references, or demonstratives presented by Defendants. I may also testify on opinions expressed by other experts or percipient experts.

3. I reserve the right to supplement or amend this report if additional facts and information that affect my opinions become available. It is my understanding that Plaintiffs have retained other experts and that Defendants may serve an expert report concerning one or more of the issues I address in this report. I reserve the right to testify concerning such other reports or testimony, and to respond to any such report from Defendants' expert(s) and to rebut at trial any opinions expressed in such a report. I also understand that depositions of additional fact witnesses may take place and that Defendants have just recently produced or will be producing additional documents that are still undergoing review. Furthermore, it is my understanding that Defendants are still in the process of producing documents, and have produced, and continue to produce, a substantial quantity of documents and other information in formats that are inaccessible or exceedingly difficult to access or evaluate properly, and that Plaintiffs' counsel is

continuing to attempt to obtain and convert such information into a usable format. Should Plaintiffs' counsel's efforts be successful and information from any of these sources becomes available to me, I reserve the right to supplement this report to incorporate my evaluation of that information.

4. The headings in this report have been added to create sections for ease of organization. I do not intend these headings to be in any way restrictive of the information contained in the respective sections.

B. Compensation

5. I am being compensated for my work on this matter at my customary rate of $400 per hour, plus expenses. I am being compensated for travel time at a rate of $300 per hour and for deposition or other testimony at a minimum daily fee of $1500. My compensation is not conditioned on the substance of my opinions, testimony at deposition or trial, or the outcome of this matter.

II. BACKGROUND AND QUALIFICATIONS

6. I earned my Bachelor of Science degree in biology *cum laude* in 1991 from Yale University, where I was named a Yale University Richter Fellow. I was awarded my M.D. by Northwestern University in 1995. Following medical school, I gained post-graduate training through residencies with the Naval Hospital San Diego (surgery) and the University of Massachusetts Medical School (emergency medicine). In addition, I completed a two-year fellowship in toxicology with the University of Massachusetts Medical School.

7. I served as an active duty U.S. Navy officer for four years, and served as a U.S. Navy Flight Surgeon with the U.S. Marine Corps in Okinawa, Japan.

8. I began my independent clinical and research career in the Department of Emergency Medicine at the University of Massachusetts Medical School in 2002. I was promoted to Assistant Professor of Emergency Medicine in 2004, and to Associate Professor in 2010. In addition, I currently serve as Program Director of the Emergency Medicine Residency Program and as Vice Chair of Education for the Department of Emergency Medicine at the University of Massachusetts Medical School. I also work as an Attending Emergency Physician

at the University of Massachusetts Medical Center, Marlborough Hospital, and Clinton Hospital. I am actively involved with numerous professional committees within the University of Massachusetts, including the Department of Emergency Medicine Research Committee, and in national and international scientific organizations, such as the Society for Academic Emergency Medicine and the America College of Emergency Physicians.

9. I am certified by the American Board of Emergency Medicine and the American Board of Toxicology. I currently hold a license to practice medicine in Massachusetts.

10. During my professional career, I have received a number of awards, including the Navy and Marine Corp Achievement Medal, the Society for Academic Emergency Medicine ("SAEM") Best Resident Basic Science Presentation Award, the SAEM New England Regional Research Directors Excellence in Research Award, and a Young Investigator Award from the Society for Academic Emergency Medicine.

11. I am an emergency physician and medical toxicologist, with both a clinical and research focus on the toxicity of acetylcholinesterase inhibitors, and the clinical evaluation and treatment of exposures to these agents, including therapies involving administration of anticholinergics and cholinesterase reactivators. A major focus of my research has been the toxicity of organophosphorus pesticides. To that end, I have performed clinical research related to organophosphorus pesticides in Sri Lanka, and through my training and clinical practice, I believe I have treated more organophosphorus-poisoned patients than any other physician in North America. I have been the Principal Investigator on grants from the NIH and other institutions totaling more than $1.8 million, related to the toxicity of organophosphorus pesticides, as well as the clinical evaluation and treatment of organophosphorus-poisoned patients.

12. I have published more than 35 original research articles in peer reviewed journals, review articles, and book chapters. I have been invited to present my research, particularly on the clinical effects of and treatments for exposure to anticholinesterase agents, at numerous professional meetings both in the United States and internationally. I serve on the editorial boards of two journals in the fields of emergency medicine and toxicology, and on the manuscript

review list for several others. A current copy of my *curriculum vitae* is attached hereto as Exhibit 1, which includes a complete list of my publications to date.

III. BASIS AND SCOPE OF MY OPINIONS

13. I have been asked to provide my opinions regarding the risk of long-term health effects that may result from acute or sub-chronic exposure to the following classes of compounds, including, but not limited to, the exemplary chemicals listed below.[1]

Class	Exemplary Agents
Acetylcholinesterase (AChE) Inhibitors	<u>Organophosphorus (OP) Nerve Agents</u> • VX • Sarin • Soman • Tabun • GF • GD • EA 3148 <u>Organophosphorus Pesticides</u> • DFP • TEPP • Malathion <u>Carbamates</u> • Physostigmine • Prostigmine • Pyridostigmine <u>Other AChE Inhibitors</u> • Mylaxen • Tacrine
Cholinesterase Reactivators	• 2-PAM • P2S • TMB-4

[1] Chemical names, alternative names, and chemical structures for these agents are shown in *Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents*, Vol. 1 (Anticholinesterases and Anticholinergics), National Academy Press, 1982, at Appendices A and B; *Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents*, Vol. 2 (Cholinesterase Reactivators, Psychochemicals, and Irritants and Vesicants), National Academy Press, 1984, at 5. Some of these substances or analogs of these substances may have been denominated by code names, most of which begin with an "EA" prefix, which are also intended to be encompassed within the scope of the opinions in this report.

Anticholinergic Compounds	<u>Glycolates</u> • BZ • EA 3443 • EA 3834 • EA 3580 • EA 3167 • Compound 302,196 • Compound 302,668 • Ditran <u>Tropane Alkaloids</u> • Atropine • Scopolamine

14. The compounds within each class listed exhibit marked commonalities such that it is appropriate to discuss the compounds in terms of classes, with focus on some of the more important or characteristic ones. Therefore, my evaluation includes a discussion of each of the chemical classes of compounds listed above, their chemical properties and modes of pharmacological action, and acute clinical effects and long-term health effects that may result from acute exposure to these agents. I have included some discussion of particular notable or representative compounds from each class.

15. In particular, I have been asked to opine whether the service members exposed to the chemical agents listed above during Defendants' human test experiments would be at an increased risk of developing adverse long-term health effects. My evaluation includes a consideration of available information concerning the doses and pathways of exposure used in the testing on military subjects, and the relevance of these parameters to the risks of both short- and long-term health effects. With respect to the doses and pathways of exposure, I have reviewed data drawn from several sources, including technical reports and other documents from Edgewood Arsenal,

excerpted data from the Chem-Bio Database that was provided to me, and a book written by one of the principal researchers at Edgewood Arsenal, Dr. James Ketchum. I have been asked to provide my opinion how the risks of developing adverse long-term health effects would be affected by exposure of test subjects to multiple doses of a given agent or to doses of multiple

chemical agents, including those specifically reviewed here as well as others that I understand were tested during Defendants' testing programs.

16. I have been asked to review the Department of Veterans Affairs Outreach Letter (VET001_015129-130), the Department of Defense Fact Sheet (VET001_015131-132), and the Frequently Asked Questions (VET001_015133-134) document, and to provide my medical opinion regarding certain statements made in these documents.

17. I have been asked to provide my medical opinion regarding the impact that preventing test subjects from discussing with their medical practitioners the substances and doses to which they were exposed could have on diagnosis and treatment of any long-term health problems that resulted from the exposures.

18. Finally, I have been asked to provide my opinion regarding the nature of suitable follow-up measures for monitoring veterans exposed to the chemical agents discussed in this report, and the relevance of a lack of such a program on the health risks faced by exposed veterans.

19. In arriving at my opinions in this matter, I have relied upon the types of information and resources that are normally relied upon by experts in my field. I have relied on my knowledge, experience, and training in the fields of emergency medicine and medical toxicology, my review of documents provided to me by counsel in this matter, as well as information reported in peer-reviewed research articles. A list of the documents I have reviewed and relied upon, in whole or in part, is attached as Exhibit 2. I reserve the right to provide further exhibits to be used as a summary of or as support for my opinions.

IV. SUMMARY OF OPINIONS

20. For the reasons described in this report, it is my opinion that the testing program subjects who were exposed to AChE inhibitors, cholinesterase reactivators, or anticholinergic agents, either through a single dose or repeat dosing, or in combination with other neurologically-active substances, suffer an increased risk of long-term adverse health effects. Because these agents act through multiple, complex mechanisms, the increased risks are not limited to situations

in which acute toxicity is observed. Participation in the testing program increases the risk of PTSD and other psychological impacts, irrespective of dose received.

21. In my view, the Department of Veterans Affairs Outreach Letter and related documents include a number of scientifically and medically inaccurate statements.

22. Finally, it is my opinion that in order for the testing program participants to receive proper ongoing health care and monitoring, each participant must be made aware of the precise nature of the tests in which he was involved. Ideally, these test subjects would be monitored through a comprehensive medical follow-up program administered by the agencies with first-hand information about the tests.

V. OVERVIEW OF TESTING PROGRAM

23. Between World War I and about 1975, tens of thousands of military service members were used as subjects in a wide-reaching testing program to study more than 400 chemical and biological warfare agents. Chemical Warfare Agent Experiments Among U.S. Service Members, Dept. of Veterans Affairs, Washington, D.C., updated 2006 (hereinafter "CWA Experiments"), at VET001_015677; VBA Outreach Efforts to Veterans Exposed to Chemical and Biological Substances, August 2008, at DVA003 010051-2. As part of this program, more than 7100 U.S. soldiers were subjected to chemical, biological, and psychological warfare agent testing at Edgewood Arsenal between 1950 and 1975. VBA Outreach Efforts at DVA003 010051; *Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents,* Vol. 1 (Anticholinesterases and Anticholinergics), National Academy Press, 1982 (hereinafter "*NRC Report Vol. 1*"), at x. The test agents generally fall into a number of categories, including, for example: 1) the acetylcholinesterase inhibitors (such as sarin, VX, soman, tabun, and physostigmine); 2) anticholinergic agents (such as BZ, synthetic BZ analogs, atropine, and scopolamine); 3) cholinesterase reactivators (such as 2-PAM and P2S); 4) irritant and blistering agents (such as sulfur mustard); 5) psychological agents (such as LSD and related derivatives); 6) other chemical agents; and 7) biological substances. "Agent/Stimulant Name," DVA003 010053-64. This report principally focuses on the acetylcholinesterase inhibitors, the cholinesterase reactivators, and the anticholinergics.

24. Long-range objectives of these human chemical tests included the goal "to improve point and area coverage either by increase in toxicity of the agents or by vastly improved dissemination methods or both." Meeting of U.S. Army Chemical Corps Advisory Council, 23-24 June 1958, Army Chemical Center, Maryland, at p. 61. Another aim of the research was to determine methods for protecting soldiers in the event of exposure to various chemical warfare agents. *NRC Report Vol. 1* at 1. Notably, however, "[t]he physiological effects of compounds of potential interest" to the researchers at Edgewood Arsenal ranged "from *high lethality to temporary incapacitation without lethality*." Witten, B., "The Search for Toxic Chemical Agents," Edgewood Arsenal Technical Report, EATR 4210, November 1969 (hereinafter "EATR 4210"), at VET013-005587 (emphasis added). Persistent lethal agents were seen as useful in particular tactical situations, while nonlethal, quick-acting incapacitating agents were useful in others. EATR 4210 at VET013-005587. An objective of the research was to identify a family of agents that would "produce a variety of effects ranging from mild incapacitation to death." EATR 4210 at VET013-005587.

25. Researchers at Edgewood Arsenal developed a systematic toxicity screen to aid in identifying promising chemicals with lethal effects. EATR 4210 at VET013-005589. Compounds of interest were those that exhibited an intravenous LD_{50} in the mouse of less than 0.1 mg/kg, in rabbits an intravenous LD_{50} of less than 0.025 mg/kg for anticholinesterases or less than 0.2 mg/kg for compounds with other mechanisms of lethality, percutaneous toxicity in rabbits of less than 2 mg/kg, and an intravenous LD_{50} in dogs of less than 0.025 mg/kg. EATR 4210 at VET013-005590. Promising lethal and incapacitating leads were identified by these and other screening experiments, and analogs were then synthesized in an effort to identify a compound with optimal properties. EATR 4210 at VET013-005591. As a result of these studies, the nerve gases sarin and VX were identified as lethal agents, and BZ as an incapacitating agent, and these compounds were standardized and stockpiled by the United States. EATR 4210 at VET-005592. It is clear that the primary objectives of Defendants' chemical warfare testing program included the identification of lethal agents.

VI. ACETYLCHOLINESTERASE INHIBITORS

A. Military Interest in Acetylcholinesterase Inhibitors

26. Acetylcholinesterase inhibitors are a structurally diverse class of compounds composed primarily of the military nerve agents (such as tabun, sarin, soman, and VX), the organophosphorus (OP) pesticides (such as malathion), and the carbamates (such as physostigmine).

Sidell, F.R., "Nerve Agents," in Medical Aspects of Chemical and Biological Warfare, Sidell, F.R. *et al.* (eds.), Chapter 5, Office of The Surgeon General, Washington DC, 1997, (hereinafter, "Sidell/Nerve Agents"), at VET004_001215.

27. The organophosphorus nerve agents, including sarin, soman, and tabun, were first synthesized by German scientists in the 1930s and 1940s as agricultural insecticides. Sidell/Nerve Agents at VET004_001215.

These nerve agents were "designed specifically to cause incapacitation or death in military use and are particularly effective because of their extremely high acute toxicity." Munro, N.B. *et al.*, "Toxicity of the Organophosphate Chemical Warfare Agents GA, GB, and VX: Implications for Public Protection," Environmental Health Perspectives, 1994, 102(1), 18-38 (hereinafter, "Munro"), at 18.

28. The carbamate physostigmine was originally isolated in the late 1800s as the pharmacologically active component of the Calabar bean and was first synthesized in the 1930s. Sidell/Nerve Agents at VET004_001215; Julian, P.L. and Pikl, J. *J. Am. Chem. Soc.* 1935, 57, 539. Carbamates of this type, including physostigmine and pyridostigmine, were initially developed and have been used as treatments for myasthenia gravis and glaucoma. Sidell/Nerve Agents at VET004_001215, 1217.

29. Following World War II and the discovery that Germany had been engaging in extensive chemical warfare research, the U.S. and the UK military organizations initiated large research programs to develop these compounds for military applications. Sidell, F.R., "A History of Human Studies with Nerve Agents by the UK and USA," in *Chemical Warfare Agents: Toxicology and Treatment*, *supra,* Chapter 9, at 223. In the U.S., research involved studies in animal models as well as administration to both military personnel and civilian subjects. *Id.* at 224. By the 1950s and 1960s, the U.S. had begun to produce stockpiles of sarin and VX for potential military use. Sidell/Nerve Agents at VET004_001216. Ultimately, according to Edgewood Arsenal researchers, military interest in these agents as potential incapacitating agents waned because of their unacceptable safety margins, *i.e.*, the ratio of the lethal dose to the incapacitating dose was too low. Ketchum, J.S. and F.R. Sidell, "Incapacitating Agents," in Military Medicine, Chapter 11, at VET004_000488.

B. Mechanisms of Action

30. Knowledge about the mechanisms of action, effective and lethal doses, and pharmacological effects of acetylcholinesterase inhibitors has flowed from both animal and human studies. Examples of such studies include military-sponsored studies on nerve agents, pesticides, and carbamates, as well as studies of victims of accidental or occupational exposures to these agents. Because nerve agents and OP pesticides have similar structural features, mechanisms of action, and basic toxicological profiles, the OP pesticide scientific literature is directly relevant to a general evaluation of potential short- and long-term health effects from organophosphorus nerve agent exposure. Notably, however, the "acute toxicity [of the nerve agents] is three to four orders of magnitude greater than most of the chemically similar OP pesticides…." Munro at 18. In addition, because of the similarities in mechanisms of action between the carbamates and OP agents, studies of the OP compounds can inform the analysis of potential health effects for the carbamates.

31. Anticholinesterase agents exert their pharmacological effects on the cholinergic nervous system through inhibition of the enzyme acetylcholinesterase ("AChE"). During nerve transmission, the neurotransmitter acetylcholine ("ACh") is released from the pre-synaptic nerve

into the synaptic cleft. Receptors on the post-synaptic neural membrane bind acetylcholine, thereby relaying the signal. AChE hydrolyzes ACh to choline, which is reabsorbed by the pre-synaptic nerve, terminating the signal transmission. Sidell/Nerve Agents at VET004_001218-19. By controlling the concentration of acetylcholine at nerve junctions, the enzyme plays a critical role in normal signal transduction between neurons in both the central and peripheral nervous systems. *NRC Report Vol. 1* at 5. Chemicals that inhibit or inactivate AChE allow ACh to accumulate in the intraneuronal space, effectively leading to a state of continuous nerve stimulation. *Id*.; Sidell/Nerve Agents at VET004_001219.

32. Acetylcholine binds to both muscarinic and nicotinic types of receptors in the cholinergic nervous system. Sidell/Nerve Agents at VET004_001218. Muscarinic receptors are found on end-organs innervated by postganglionic parasympathetic fibers and in the central nervous system (CNS). *Id.* Parasympathetic neurons primarily innervate smooth muscles and exocrine glands via some of the cranial and sacral nerves, which in turn innervate intraocular muscles; lacrimal and nasal glands; salivary glands; bronchial muscles and glands; the heart; muscles of the gut; and the bladder. *Id.* In general, activation of these parasympathetic targets results in contraction of smooth muscle and excessive secretion. *Id.* Nicotinic receptors are found at the neuromuscular junction (NMJ) of somatic muscle (skeletal muscles) and at all autonomic ganglia (sympathetic and parasympathetic), transmitting signals from preganglionic autonomic neurons to postganglionic neurons. *Id.* There are also nicotinic receptors in the CNS.

33. Like natural ACh, AChE inhibitors react with the target enzyme to form a covalent complex; while the ACh-enzyme complex is hydrolyzed very rapidly to regenerate the active enzyme, the inhibitor complexes are hydrolyzed at a much slower rate. The complexes that result from exposure to "reversible" inhibitors, such as physostigmine, have a half-life on the order of 40 million times that for ACh (*e.g.*, 30 minutes compared to 42 μs). *NRC Report Vol. 1* at 9. The "irreversible" inhibitors, such as the organophosphorus agents, generate a stable, phosphorylated complex with the enzyme that breaks down slowly over days or even months. *Id.* For some phosphorylated enzymes, the enzyme regeneration rate can be so slow that the phosphorylated AChE is effectively rendered inactive. Furthermore, some of these phosphorylated enzymes can

degrade over a variable period of time (minutes to days) in a process called "aging." An aged enzyme is permanently phosphorylated and cannot be regenerated by spontaneous hydrolysis or exposure to an antidote; recovery of AChE function at this stage can only occur through synthesis of new enzyme. *Id.* at 11-12.

34. Most acetylcholinesterase agents exert activities other than acetylcholinesterase inhibition that may contribute to their toxic effects. For example, AChE agents may also interact with other neurotransmitters, or with enzymes, ion channels, or sites on muscle tissue. Reutter, S.A. et al., Evaluation of Airborne Exposure Limits for VX: Worker and General Population Exposure Criteria (hereinafter "Reutter"), VET013-012724 at VET013-012740; Sidell/Nerve Agents at VET004_001218.

35. The organophosphorus nerve agents also can function as alkylating agents, and therefore are capable of reacting irreversibly with biological macromolecules, such as DNA. *NRC Report Vol. 1* at 5, 16, 27-28; Wooder, M.F. and A.S. Wright, "Alkylating of DNA by Organophosphorus Pesticides," *Acta Pharmacol. Toxicol. (Copenh).* 1981, 49(Suppl 5), 51-55. As scientific studies regarding genotoxicity or mutagenicity of these compounds as a class is lacking, such reactivity cannot be ruled out.

C. Acute Clinical Effects from Exposure to Acetylcholinesterase Inhibitors

36. Because of their common primary mechanism of action, the acute toxic effects of acetylcholinesterase inhibitors are qualitatively similar among individual compounds within the class, and among humans and animals. *NRC Report Vol. 1* at 21. Quantitative differences in clinical effects, including the particular constellation and severity of symptoms, time of onset, and duration of effect, are a function of the chemical structure and inherent potency of the compound, volatility of the compound, the dose given, individual susceptibility, and the route of administration. *Id.*; Sidell/Nerve Agents at VET04_001225-1228. Notably, because these compounds act on a range of neuronal enzymes and receptors, significant individual variations in sensitivity exist, perhaps due to differences in endogenous levels of target enzymes and receptors. Munro at 34. In addition, the symptomatic or systemic reaction to a single dose of a given agent

may be altered, even exacerbated, by chronic or sub-chronic administration of same agent, another agent in the same mechanistic class, or an agent that acts by a different mechanism.

37. For AChE inhibitors, the chemical structure of the individual agent determines the affinity with which it covalently binds to the enzyme, and how slowly the active enzyme is regenerated by hydrolysis. In addition, the chemical structure affects the absorption, distribution, and metabolism of the agent, and thus, the persistence of its effects. For example, physostigmine and the nerve agents are readily absorbed when administered by almost any route, including by oral, intravenous, subcutaneous, dermal, or inhalation. *NRC Report Vol. 1* at 7; Potential Military Chemical/Biological Agents and Compounds, Field Manual 3-11.9, January 2005 (hereinafter "FM 3-11.9"), VET013-004661 at 4852; EATR 4210 at VET013-5597-5598. Many of these agents are highly lipid soluble and bind to blood and tissue proteins; these mechanisms may allow the chemical agents to persist systemically over a long period of time. Some of the OP nerve agents are "essentially colorless, odorless, tasteless, and nonirritating to the skin," and therefore, an exposed subject may not be aware of the exposure until acute or delayed clinical effects appear. Munro at 20.

38. In the periphery, acute exposure to AChE inhibitors leads to excess secretion of glands that are innervated by postganglionic cholinergic fibers, including those of the bronchioles, sweat glands, lacrimal glands, salivary glands, and others of the GI tract. Acute cholinergic poisoning symptoms usually develop within minutes or hours of exposure, and include miosis (pupil contraction), rhinorrhea (runny nose), salivation, headache, dizziness, nausea, sweating, anxiety, and restlessness. *NRC Report Vol. 1* at 21; Treatment of Chemical Agent Casualties, Technical Manual No. 8-285, 15 Jan. 1968 (hereinafter "TM 8-285", JK02-0002994 at JK02-0003010; Reutter, VET013-012724 at VET013-012744. Life-threatening symptoms may include weakness, tremor, uncoordination, convulsions, vomiting, bronchoconstriction and excessive bronchosecretions, difficulty breathing, diarrhea, abdominal cramping, and urinary and bowel incontinence. *NRC Report Vol. 1* at 21; TM 8-285 at JK02-0003010; Reutter, VET013-012724 at VET013-012744. Effects of excessive ACh at neuromuscular junctions are also complex and include prolonged depolarization of the motor end-

plate. This overstimulation leads to muscle fasciculations, involuntary twitching, and eventually to muscle fatigue, weakness, and paralysis. Reutter, VET013-012724 at VET013-012744. Functional and ultrastructural changes of the NMJ also occur. *NRC Report Vol. 1* at 21.

39. Respiratory failure is considered to be the major factor leading to death from exposure to AChE inhibitors, and is caused by hyperacute central respiratory apnea; increased airway resistance due to bronchoconstriction and a markedly increased amount of secretions; and progressive respiratory muscle weakness and paralysis. *NRC Report Vol. 1* at 22. If untreated, respiratory muscle weakness progresses, causing hypoxia and respiratory muscle paralysis. *Id.*

40. The cardiovascular effects of AChE inhibitors are complex and variable. The principal direct effect of ACh transmission on the heart leads to bradycardia. TM 8-285 at JK02-0003010. However, at the sympathetic ganglionic level, ACh is the primary neurotransmitter, and elevated levels of ACh lead to increases in epinephrine and norepinephrine, which in turn increase heart rate. Thus, there are competing sympathetic and parasympathetic effects on the cardiovascular system. In general, however, acutely exposed patients demonstrate bradycardia and, in severe cases, hypotension and potentially, cardiogenic shock. NRC Report Vol. 1 at 22.

41. AChE inhibitors have significant effects on the CNS, including behavioral and cognitive changes, impaired consciousness or coma, seizures, or central apnea. TM 8-285 at JK02-0003010. In particular, acute toxic effects include confusion, ataxia, slurred speech, loss of reflexes, coma, irritability, anxiety, depression, fatigue, insomnia, and nightmares, and impaired judgment, concentration, or memory. *NRC Report Vol. 1* at 21; Ohbu, S. *et al.* "Sarin poisoning on Tokyo subway," *South. Med. J.* 1997, 90, 587-93; Kawana, N. *et al.* "Psycho-physiological effects of the terrorist sarin attack on the Tokyo subway system," *Mil. Med.* 2001, 166, 23-6. These symptoms may persist chronically after acute exposure. *NRC Report Vol. 1* at 21.

42. At high doses, AChE inhibitors rapidly cause seizures, which, if left untreated, can cause permanent neurological and cardiac damage in those subjects who survive. Munro at 27 and 29. In experimental animals, morphologic brain injury is not isolated to one area, but changes can be seen in cortical regions, amygdala, hippocampus, cingulate gyrus, and the thalamus. McDonough, J.H., Jr. *et al.* "Neural Lesions in the Rat and Their Relationship to EEG

Delta Activity Following Seizures Induced by the Nerve Agent Soman," Neurotoxicology 1998, 19, 381-91.

43. Several chemical agents, including atropine, 2-PAM, and benzodiazepines (such as diazepam), are used to treat acute poisoning by AChE inhibitors. While these antidotes may prevent death in exposed animals, they fail to combat all the mechanisms by which the AChE inhibitors exert their toxic effects. *NRC Report Vol. 1* at 22. For example, atropine reduces the exposure of central muscarinic neurons to elevated ACh levels, but has no effect on nicotinic receptors. *Id.* Similarly, oxime cholinesterase reactivators such as 2-PAM do not penetrate the blood-brain barrier and therefore have no ameliorative effect on cholinergic synapses in the CNS. *Id.* Benzodiazepines have variable ability to prevent seizures and morphological CNS damage. Shih, T.-M. *et al.*, "Control of Nerve Agent-Induced Seizures is Critical for Neuroprotection and Survival," *Toxicol. Appl. Pharmacol.* 2003, 188(2), 69-80.

44. The route of administration affects the actual dose received by the subject, and is relevant to the severity and range of acute and chronic clinical effects (*e.g.*, local or systemic).

FM 3-11.9 at VET013-004720 and 4864;

Cannard, K., "The Acute Treatment of Nerve Agent Exposure," *J. Neurol. Sci.* 2006, 249, 86-94, at 89; Sidell/Nerve Agents at PLTF 002476. The dose effective to cause severe effects, including some deaths, in 50% of subjects (ED_{50}) by percutaneous administration is 2 mg (equivalent to 29 µg/kg for a 70 kg human). FM 3-11.9 at VET013-004720 and VET-013-004864.

To put the toxicity of VX in perspective, an amount of the nerve agent the size of a drop of water placed on the skin will kill 50% of exposed people.

45. Sarin, soman, and tabun are less toxic than VX, but each is still a lethal agent. The LD_{50} for sarin in humans is 1.7 g (equivalent to 24 mg/kg for a 70-kg human) for dermal exposure, and the LCt_{50} is 100 mg-min/m^3 for vapor exposure. Sidell/Nerve Agents at VET004_001227; Cannard 2006 at 89; Witten at VET013-005598-99. Threshold symptoms are observed at a vapor dose of 2 mg-min/m^3, and mild incapacitation is effected at a vapor dose of 15 mg-min/m^3 under the same conditions. Witten at VET013-005598-99.

46. The LD_{50} for soman is about 350 mg, or about 5 mg/kg, for percutaneous exposure, and the effective dose (ED_{50}) for severe effects is 3 mg/kg. "Soman," in Review of Acute Human-Toxicity Estimates for Selected Chemical-Warfare Agents, Committee on Toxicology, National Research Council, Chapter 4, VET001_010053 at 10056-10057.

Sidell, F.R., "Soman and Sarin: Clinical Manifestations and Treatment of Accidental Poisoning by Organophosphates," Clinical Toxicology 1974, 7(1), 1-17 (hereinafter "Sidell/Soman and Sarin"), JK07 0012043 at 12044;

For this reason, oxime antidotes are largely ineffective in treating soman poisoning.

47. Tabun exerts its toxic effects rapidly upon systemic exposure, and exposure also occurs through skin contact, eye contact, or inhalation. The LD_{50} in humans is 1 g for dermal

exposure, and the LCt_{50} is 400 mg min/m^3. Sidell/Nerve Agents at PLTF 002476.

48. Studies of the lethality of physostigmine in experimental animals place this agent in the "highly toxic" chemical class. For example, the median lethal dose for subcutaneous or intramuscular administration in rats was found to be 1.28 to 1.78 mg/kg. Frost, D.F. and D.W. Korte, Jr., "Acute Subcutaneous Toxicity of Physostigmine Salicylate in Sprague-Dawley Rats," Institute Report No. 313, November 1988, Letterman Army Institute of Research, at page 14.

D. Long-Term Health Effects of Acute or Sub-Chronic Exposure to Acetylcholinesterase Inhibitors

49. As a result of their actions on AChE, and possibly on the enzyme neurotoxic esterase (NTE) and other physiological structures, acetylcholinesterase inhibitors have long been known to cause long-term health effects, including psychological effects, EEG abnormalities, cardiac dysfunction, and delayed neuropathy. Munro at 27. These delayed or persistent impacts can occur even when exposures are at doses below those necessary to generate signs of acute cholinergic toxicity.

50. The weight of the literature in this area indicates that subjects may experience long-term neurological and psychiatric problems from a single exposure to an acetylcholinesterase inhibitor. *NRC Report Vol. 1* at 25; Munro at 27-29. Inhibition of brain AChE can perturb other neurotransmitter circuits in the CNS, such as the gamma-aminobutyric acid system, and systems involving peptide neurotransmitters. Reutter, VET013-012724 at VET013-012745. In a December 1999 study prepared for the U.S. Army Center for Health Promotion and Preventive Medicine at Aberdeen Proving Ground, the authors offer that the long-term effects of these agents are unknown, but acknowledge that "the circuits are so complex that even a temporary perturbation might lead to reverberations that would persist for a long time." Reutter, VET013-012724 at VET013-012745.

51. Several studies have shown long-term disorders such as affective and emotional changes, reductions in cognitive abilities, and sleep disturbances, arise from even a single exposure to an OP agent. For example, Tabershaw found that after acute poisoning, 38% of

subjects had effects on affect, emotion, and memory, and 9% of individuals reported persistent somatic complaints. *NRC Report Vol. 1* at 25; Tabershaw, I.R. *et al.*, "Sequelae of Acute Organic Phosphate Poisoning," *J. Occup. Med.* 1966, 8, 5-20. Duffy et al. examined awake and asleep EEGs on humans who had suffered occupational exposure to sarin (acute and chronic) up to one year before testing, and concluded, "[r]egardless of the pathogenic mechanisms, results of the current study confirm the ability of OP compounds to induce persistent abnormalities in the electrical activity of the human brain." Duffy, F.H. *et al.*, "Long-term Effects of an Organophosphate upon the Human Electroencephalogram," *Toxicol. Appl. Pharmacol.* 1979, 47, 161-76, at 175. AChE inhibitors may also cause developmental neurotoxicity at doses below those required to cause acute toxic effects. Jamal, G.A. *et al.*, "Low Level Exposures to Organophosphorus Esters May Cause Neurotoxicity," *Toxicology* 2002, 181-182, 23-33. See also: Metcalf, D.R. *et al.*, "EEG, Psychological, and Neurological Alterations in Humans with Organophosphorus Exposure," *Ann. N.Y. Acad. Sci.* 1969, 160, 357-65 (noting disturbed memory, reduced alertness, and narcolepsy following OP exposure); Holmes, J.H. and M.D. Gaon, "Observations on Acute and Multiple Exposure to Anticholinesterase agents," *Trans. Am. Clin. Climatol. Assoc.* 1956, 68, 86-100; *NRC Report Vol. 1* at 25-26.) Reidy and co-workers studied migrant farm workers who suffered two acute exposures to OP pesticides (one two years prior to the study and one five years prior) as well as chronic low-level exposure. Reidy, T.J. *et al.*, "Pesticide Exposure and Neuropsychological Impairment in Migrant Farm Workers," *Arch. Clin. Neuropsych.* 1992, 7, 85-95, at 88. While it was not possible with this study to separate those effects that resulted from acute versus chronic exposure, the exposed workers exhibited an array of long-term health effects relative to matched controls, including motor speed, coordination, and visuospatial memory deficits, and elevated levels of anxiety, depression, irritability, difficulty concentrating, confusion, memory problems, and physical symptomatology. *Id.* at 93. Accidental dermal exposure of a lab worker to a solution of soman led to protracted psychiatric sequelae, including depression and sleep disturbances, even up to five weeks after exposure. Sidell/Soman and Sarin, JK07 0012043 at 12046, 12048, and 12057.

52. As mentioned above, the neurodegenerative effects of AChE inhibitors, including the OP agents, have been characterized in a number of species, and these physiological effects lead to sensorimotor neuropathy, evidenced by pain, tingling in the extremities, muscle weakness, weight loss, ataxia, muscle atrophy, or muscle spasticity. *NRC Report Vol. 1* at 23-26; Petras, J.M., "Soman Neurotoxicity," *Fund. Appl. Toxicol.* 1981, 1, 242. Haggerty and Kurtz described that single dose exposure of rats to soman or VX caused "relatively long-lasting signs of toxicity such as persistent tremoring…[,] seizures, and irritability when handled[,]" and concluded that VX is a "potent nerve agent that causes behavioural changes in the rat that are marked and long lasting." Reutter, VET013-012747; Haggerty, G.C. *et al.*, "Duration and Intensity of Behavioral Change after Sublethal Exposure to Soman in Rats," *Neurobehav. Toxicol. Teratol.* 1986, 8(6), 695-702. Petras reported that acute dosing of rats with soman led to typical acute toxicity (muscle fasciculations, tremors, and seizures) and ultimately to extensive axonal and terminal degeneration in the limbic, corticofugal, and central motor system regions of the brain. Petras at 242.

53. Some organophosphorus compounds cause organophosphorus-induced delayed neuropathy (OPIDN), at least in part due to their actions against NTE, an effect that is independent of a given agent's ability to inhibit AChE. Reutter at VET013-012748-9; *NRC Report Vol. 1* at 23-24; Petras at 242. Notably, effects arising by this mechanism, such as weakness, tingling, muscle twitching, and severe sensorimotor neuropathy, may not begin to appear until one to three weeks after exposure, and can result even from a single exposure. Munro at 27; *NRC Report Vol. 1* at 23-24. OPIDN is a recognized phenomenon for some OP pesticides but occurs much less frequently with the nerve agents, and at much higher doses. Sidell, F.R., "Longterm Health Effects of Nerve Agents and Mustard," Medical Aspects of Chemical and Biological Warfare, *supra*, Chapter 8 (hereinafter "Sidell/Health Effects"), VET004_001168 at 1171. In particular, OP poisoning has been shown to lead to axonal degeneration and loss of myelin sheathing on both peripheral and central nerves. *NRC Report Vol. 1* at 24. Unlike acute effects, these delayed effects are unlikely to resolve due to the degenerative nature of the disease progression.

54. Exposure to acetylcholinesterase agents, including nerve agents (such as sarin, soman, and tabun) and OP pesticides, has been shown to cause necrosis of skeletal muscle, including swelling, eosinophilia, and loss of striations of myofibers. Sidell/Health Effects at VET004_001172.

55. Acute exposure to nerve agents also may lead to persistent psychological effects that do not correlate with the dose received. The Japanese cult Ayun Shinrikyo used sarin as a means of domestic terrorism in two separate attacks in 1994 and 1995, and these events have provided an excellent source of information on long-term effects on humans from acute exposure to nerve agents. In the first attack, seven people died and over 250 people were affected or sought care. Suzuki, J. *et al.*, "Eighteen Cases Exposed to Sarin in Matsumoto, Japan," *Intern. Med.* 1997, 36, 466-70.) Although the first attack was not well-publicized outside Japan, the second attack received significant media attention. In the second attack, Ayun Shinrikyo members released sarin liquid in three subway trains converging on Kasumigaseki Station in Tokyo. After this attack, 11 people died and more than 5000 people sought medical attention. Okumura, T. *et al.*, "Report on 640 Victims of the Tokyo Subway Sarin Attack," *Ann. Emerg. Med.* 1996, 28, 129-35.

56. Victims of these sarin attacks were found to have poorer performance on psychological and psychomotor testing, in addition to having findings consistent with post-traumatic stress disorder (PTSD),[3] at timepoints up to seven years after exposure. Okumura, 1996, *supra*; Yokoyama, K. *et al.*, "Chronic Neurobehavioral and Central and Autonomic Nervous System Effects of Tokyo Subway Sarin Poisoning," *J. Phys. (Paris)* 1998, 92, 317-23; Miyaki, K. *et al.* "Effects of Sarin on the Nervous System of Subway Workers Seven Years after the Tokyo Subway Sarin Attack," *J. Occup. Health* 2005, 47, 299-304; Okumura, T. *et al.*, "Acute and Chronic Effects of Sarin Exposure from the Tokyo Subway Incident," *Environ. Toxicol. Pharmacol.* 2005, 19, 447-450; Nishiwaki, Y. *et al.*, "Effects of Sarin on the Nervous

[3] I understand that a detailed evalaution of possible long-term psychological effects, such as PTSD, from exposure to chemical warfare agents, is presented by Plaintiffs' expert, Una McCann, M.D.

System in Rescue Team Staff Members and Police Officers 3 Years after the Tokyo Subway Sarin Attack," *Environ. Health Perspect.* 2001, 109(11), 1169-1173; Murata, K. *et al.*, "Asymptomatic Sequelae to Acute Sarin Poisoning in the Central and Autonomic Nervous System 6 Months after the Tokyo Subway Attack," *J. Neurol.* 1997, 244, 601-606. Critically, these long-term effects were observed in victims who lacked any obvious clinical abnormalities at the time of testing. Murata, *supra*, at 601. In addition, victims of the attacks exhibited eye problems, fatigability, and headache one year after exposure. Okumura 2005, at 449. These findings are consistent with those of Rosenstock *et al.* who found that after an episode of exposure to OP pesticides, individuals performed poorer than controls in a range of neuropsychological tests, including auditory attention, visual memory, visuomotor speed, sequencing and problem solving, and motor steadiness, reaction, and dexterity, on average two years after the exposure. Rosenstock, L. *et al.*, "Chronic central nervous system effects of acute organophosphate pesticide intoxication," *Lancet* 1991, 338, 223-7. Hashemian and co-workers studied civilian victims of the Iran-Iraq War 17 years later, and found a signficantly increased incidence of PTSD, anxiety, and severe depressive symptoms in civilians exposed to chemical warfare relative to those exposed to conventional warfare. Hashemian, F. *et al.*, "Anxiety, Depression, and Posttraumatic Stress in Iranian Survivors of Chemical Warfare," *JAMA* 2006, 296(5), 560-566.

57. Other studies have reported prolonged changes in psychological function follow from acute exposure to sarin. Munro at 28. Studies of acute exposure have noted depression, insomnia, excessive dreaming, nightmares, and EEG changes. Munro at 28-29. Notably, workers who had previously suffered OP pesticide intoxication were found to show statistically significant deficits in intellectual ability, academic skills, abstract thinking ability, and speed and coordination in motor skills tests. Munro at 29. In addition, the exposed workers showed more depression, irritability, confusion, and tendency for withdrawal, and had difficulty with memory, thinking ability, and language use, on an average of nine years after exposure. Munro at 29. Subtle but relevant changes in EEG function were observed in patients even at six years post-exposure. Munro at 29.

58. Cardiac dysfunction is another potential long-term effect of AChE exposure. While for some agents, such as sarin, cardiac lesions in rats have been noted only in animals subjected to doses sufficient to cause convulsions, acute exposure to VX caused cardiac arrhythmias in rats and dogs even at doses below those necessary to induce convulsions. Munro at 29-30. Ventricular arrhythmias have been observed in humans poisoned by OP insecticides. Munro at 30.

59. Studies of the effects of chronic dosing of organophosphorus toxins also provide an indication of potential toxic effects that may arise from short-term exposures. Studies describing long-term effects from chronic organophosphorus agent exposure are consistent with those discussed above for acute or sub-chronic exposures. These studies demonstrate that persistent neurological, neuropsychiatric, and other long-term effects can follow from such exposure. Santolucito demonstrated that chronic exposure to AChE inhibitors at non-lethal doses also causes chronic changes in sleep patterns and electronencephalogram (EEG) recordings. Santolucito, J.A. *et al.*, "EEG of Rhesus Monkeys Following Prolonged Low-Level Feeding of Pesticides," *Toxicol. Appl. Pharmacol.* 1971, 19, 147-54. A Lancet report published in 1961 concluded that long-term difficulties with memory, concentration, and affective disorders occur after chronic exposure to OP pesticides. Gershon, S. *et al.*, "Psychiatric Sequelae of Chronic Exposure to Organophosphorus Insecticides," *Lancet* 1961, 1, 1371-4. Several studies have shown persistent deficits in cognitive function in workers chronically exposed to pesticides. For example, humans exposed to daily injections of DFP (a commonly studied OP pesticide and a precursor used in synthesis of some nerve agents) experienced insomnia, emotional lability, paresthesias, tremors, and visual hallucinations. Grob, D. *et al.*, "The Administration of Di-isopropyl Fluorophosphate (DFP) to Man; Effect on the Central Nervous System with Special Reference to the Electrical Activity of the Brain," *Bull. Johns Hopkins Hosp.* 1947, 81, 257-66. Similar results have been documented in other published case reports and series. Dille J.R. *et al.*, "Central Nervous System Effects of Chronic Exposure to Organophosphate Insecticides," *Aerosp. Med.* 1964, 35, 474-8; Midtling, J.E. *et al.*, "Clinical Management of Field Worker Organophosphate Poisoning," *West. J. Med.* 1985, 142, 514-8.

60. Recent research has also focused on the effect of AChE inhibitor exposure on the neurocognitive development of children. In recent research, it was found that 7-year-old children with the highest in-utero exposure to OP pesticides had IQ scores roughly seven points lower than children with little OP exposure. Bouchard, M.F. *et al.*, "Prenatal Exposure to Organophosphate Pesticides and IQ in 7-Year-Old Children," *Environ. Health Perspect.* 2011, 119, 1189-95. Similarly, Engel *et al.* found that exposure to organophosphorus agents was persistently and negatively associated with cognitive development of children. Engel, S.M. *et al.*, "Prenatal Exposure to Organophosphates, Paraoxonase 1, and Cognitive Development in Childhood," *Environ. Health Perspect.* 2011, 119, 1182-8. Delays in childhood cognitive development that result from exposure to other toxic substances, such as lead, have been linked to a persistent and irreversible reduction in IQ levels. Mazumdar, M. *et al.*, "Low-level environmental lead exposure in childhood and adult intellectual function: a follow-up study," *Environ. Health* 2011, 10, 24-30, at Abstract. Clearly, while some long-term neurological effects of exposure to AChE inhibitors are well-known, the full scope of effects of these agents is still underappreciated.

61. The above studies are also consistent with those of Savage et al., who evaluated a group of 100 individuals with occupationally-related OP poisoning and found abnormalities in a wide range of neuropsychological variables when compared to 100 control subjects. Savage, E.P. *et al.*, "Chronic Neurological Sequelae of Acute Organophosphate Pesticide Poisoning," *Arch. Environ. Health* 1988, 43, 38-45. Persistent abnormalities were found in neuropsychological tests of intellectual functioning, abstract thinking, and simple motor skills. Moreover, exposed subjects were twice as likely to demonstrate abnormalities on testing consistent with "cerebral damage." Furthermore, the results of exposed patients demonstrated a statistically significant increase in tests of social anxiety and other affective disorders. Lastly, the subjective effects ratings of the exposed subjects and their families suggest that the neuropsychological deficits that were demonstrated on the objective testing are also apparent in the subjects' everyday functioning.

62. As mentioned above, AChE inhibitors, by virtue of their chemical structures, are capable of alkylating key biological molecules such as DNA. Possible mutagenic effects of these

compounds, including the nerve agents and carbamates like physostigmine, in animals have not been well-studied, but the National Research Council concluded that "some may have these properties." *NRC Report Vol. 1* at 27. While the reported results are mixed, at least one study concluded certain OP nerve agents are mutagenic, which can increase the risk of cancer. *Id.* at 28. OP pesticides and nerve agents have been shown to have teratogenic and male reproductive effects as well. *Id.*; Reutter at VET013-012752.

63. The Institute of Medicine has concluded that "there is limited suggestive evidence of an association between exposure to sarin at doses sufficient to cause acute cholinergic signs and symptoms and subsequent long-term health effects." Fulco, C.E. *et al.* (eds.), Gulf War and Health: Volume 1. Depleted Uranium, Pyridostigmine Bromide, Sarin, and Vaccines, Committee on Health Effects Associated with Exposures During the Gulf War, Institute of Medicine, National Academy Press, 2000, Chapter 5 ("Sarin") (hereinafter "Fulco/Sarin") at 198-199. This committee also concluded that studies of low exposure to OP pesticides is associated with a higher prevalence of neurologic or psychiatric deficits. Fulco/Sarin at 199. The committee determined that, even in the absence of well-controlled human studies, it is "reasonable to hypothesize the occurrence of long-term adverse health effects from exposure to low levels of sarin." Fulco/Sarin at 199. Because the OP nerve agents and pesticides all exert their effects through similar mechanisms, these conclusions are reasonably applied broadly across the class of organophosphorus AChE inhibitors evaluated during the testing program.

64. The carbamate AChE compounds exert the same range of acute cholinergic effects as the OP compounds. Studies have also demonstrated long-term health impacts for the carbamates that parallel the results seen for the OP nerve agents and pesticides. For example, studies have observed short-term effects on EEG patterns in human subjects exposed to physostigmine that are consistent with the persistent changes observed in OP-exposed subjects. Pfefferbaum, A. *et al.*, "EEG Effects of Physostigmine and Choline Chloride in Humans," *Psychopharmacology* 1979, 62, 225-233, at 225, 229. Flood et al., point out that compounds like physostigmine have inconsistent impacts on, *inter alia*, memory depending on dose, method of administration, and type of memory task tested, in exposed mice. Flood, J.F. *et al.*, "Cholinergic

Receptor Interactions and Their Effects on Long-Term Memory Processing," *Brain Res.* 1981, 215, 177-185. In particular, Flood's studies are consistent with previous reports that reveal low doses of physostigmine may improve memory retention but higher doses impair retention, an impact that is attributed to changes in memory processing in the brain caused by altered ACh receptor activity. Flood, at 183-184.

65. Studies of exposure to pyridostigmine, a close chemical analog of physostigmine, are informative of the potential short- and long-term effects of exposure to the carbamate class of AChE inhibitors. Pyridostigmine was one of the most commonly tested agents at Edgewood Arsenal, and was used extensively during the Gulf War as a pre-treatment for possible nerve agent exposure. *NRC Report Vol. 1* at page 37, Table 3; Gulf War and Health, Volume 1, Chapter 6, "Pyridostigmine Bromide," at page 208. Notably, although pyridostigmine has been used for many years as a treatment for the autoimmune disorder, myasthenia gravis, exposure to this agent, alone and in combination with other factors, may contribute to the illnesses observed in Gulf War veterans. Gulf War and Health, Volume 1, Chapter 6, at 209. Pyridostigmine exposure leads to changes in neuromuscular morphology, denervation, and damage to postsynaptic and myofibrillar structures, albeit at greatly elevated doses. *Id.* at 211-212; Breyer-Pfaff, U. *et al.*, "Neuromuscular Function and Plasma Drug Levels in Pyridostigmine Treatment of Myasthenia Gravis," *J. Neurol. Neurosurg. Psychiatry* 1990, 53, 502-506, at 502.

66. As with the OP nerve agents, the carbamates induce neuro- and myopathic effects that do not correlate with AChE inhibition levels, and ultimately can lead to OPIDN or intermediate neuropathic syndromes. Gulf War and Health at 212-213. In addition, as with OP nerve agents, carbamates have been shown to cause behavioral abnormalities in rats and primates at a range of dose levels, even with a poorly brain-penetrant carbamate such as pyridostigmine. *Id.* at 213-214. Studies also indicate effects on cardiac mitochondrial function. *Id.* at 216. However, long-term follow-up studies on subjects exposed to carbamate AChEs have not been done, are poorly controlled, or lack data regarding actual exposures. Thus, the reported studies cannot rule out the possibility that acute or sub-chronic exposure to carbamate agents can lead to

an increased risk of an array of long-term physiological and neurobehavioral changes that is generally consistent with those observed for OP nerve agents.

E. Repeat Dosing and Combination Effects

67. As discussed above, each individual test agent exerts its toxic effects through mechanisms that are not completely characterized, and receiving repeated doses of a given compound or of compounds in a particular chemical class can have additional effects. Further, receiving a dose of an AChE inhibitor compound in conjunction with or in close proximity to a dose of another chemical agent may complicate the picture. Chemical compounds can influence the pharmacological and toxicological actions of other agents, for example, through pharmacological antagonism, synergism, potentiation, effects on brain penetration, or alterations in absorption or metabolic processes. Gulf War and Health: Volume 1, Chapter 6, at pages 217, 219. The synergistic effects of mixtures of anticholinesterases have been documented since the late 1950s. Frawley, J.P. *et al.*, "Marked Potentiation in Mammalian Toxicity from Simultaneous Administration of Two Anticholinesterase Compounds," *J. Pharmacol. Exp. Ther.* 1957, 121, 96-106. Indeed, the exposure of Gulf War veterans to multiple substances within these chemical classes is thought to have contributed to Gulf War syndrome. Gulf War and Health: Volume 1, Chapter 6, at page 217. In my opinion, the risk of adverse long-term health effects is likely increased when multiple doses of an AChE inhibitor are given, or when an AChE inhibitor is administered in conjunction with other pharmaceutically active toxins. In particular, because the AChE inhibitors, the cholinesterase reactivators, and the anticholinergics all exert at least some activity on the cholinergic system, exacerbated or unexpected impacts can be expected from exposure to combinations of these agents.

F. Testing of AChE Inhibitors on Military Subjects

68. At Edgewood Arsenal, at least 16 different AChE inhibitors were tested on more than 1400 subjects. *NRC Report Vol. 1* at 29, 37. Among the most frequently tested substances reported were VX (740 subjects), sarin (246), physostigmine (138), soman (83), pyridostigmine (27), and tabun (26). *Id.* at 37. Agents were administered by intravenous, vapor, oral, percutaneous, or intramuscular routes of exposure. Subjects reported a wide range of acute

effects consistent with acute cholinergic toxicity, including dizziness, frontal headache, blurred vision, lethargy, nausea, stomach pain, vomiting, rhinorrhea, chest tightness, wheezing, fasciculations, sweating (hands, feet, and site of skin contact), and significantly reduced red blood cell cholinesterase levels. *NRC Report Vol. 1* at E1-E6. AChE inhibitors, including VX, sarin, tabun, and soman, were also studied on military test subjects at other sites such as project SHAD and Project 112. CWA Experiments at VET001_015680.

69. It appears from the case excerpts summarized by the National Research Council report that the majority of test subjects displayed typical signs of acute AChE inhibitor poisoning, such as dizziness, stomach pain, blurred vision, headache, rhinorrhea, chest tightness, plasma cholinesterase depression, muscle fasciculation, drowsy, and weakness, at the test doses. *NRC Report Vol. 1* at E1-E6. Multiple dosing regimens were carried out within 1-2 days. In some cases, these were the only agents administered; in others, subjects were also dosed with a cholinesterase reactivator such as 2-PAM, P2S, or PAM chloride, or an anticholinergic agent such as atropine. *Id*. Physostigmine was often used as a "treatment" for exposure to anticholinergic agents such as BZ (discussed below), so the majority of subjects in this category were likely exposed to additional test agents, including BZ and BZ analogs, atropine, prolixin, and others.

70. Dosing ranges that were used in human experiments for each of these exemplary agents are shown in the table below:

Agent	**Exemplary Dose Ranges (Route of Administration)**
VX	
Sarin	
Soman	
Tabun	
Physostigmine	

Id. at Appendix E, E1-E5;

A more detailed discussion of exemplary testing done with each of the more commonly tested agents is presented below.

1. VX

71.

At the doses used in the testing program, test subjects would be expected to exhibit signs of acute cholinergic toxicity.

72.

2. Sarin

73.

Doses in the range would be expected to produce an array of acute toxic effects typical of nerve agents, such as runny nose, dimness of vision, mioisis, difficult breathing, abdominal cramps, involuntary defecation or urination, headache, confusion, twitching, and muscle spasms. EATR 4210 at VET013-005598. Sarin was also studied in test subjects as an experimental antidote for scopolamine dosing. Ketchum, J.S. *et al.*, "Atropine, Scopolamine, and Ditran: Comparative Pharmacology and Antagonists in Man," Edgewood Arsenal Technical Report 4761, August 1973, JK02 0004139 at 4153 and 4161.

74. Researchers at Edgewood Arsenal followed a patient who suffered an accidental exposure to sarin, and noted that at least four months after exposure, the patient still complained of chest and abdominal pains, dyspnea, restlessness, and marked depression. Sidell/Soman and Sarin at JK07 12048-51. The patient had marked EKG changes in the period immediately following exposure, and ultimately died of acute myocardial infarction, with significant cardiac anomalies. Sidell/Soman and Sarin, JK07 0012043 at 12051.

3. Soman and Tabun

75.

76.

2-PAM is clinically helpful in reducing symptoms of acute toxicity from nerve agent exposure, but this effect is thought to result from a completely separate mechanism of action, which could create its own set of health risks. Ketchum, J., "Treatment of Anticholinesterase Poisoning," in *Endocrines and Enzymes in Anesthesiology*, Ballinger, C.M. and V.L. Brechner (eds.), Springfield, Illinois, 1973, at JK02 0004016. The Edgewood Arsenal researchers were aware of this issue, noting that "oximes actually have little or no ability to reactive cholinesterase inhibited by agents such as soman, and are also unable to reverse the inhibition produced by certain carbamates." *Id.* at JK02 0004016.

4. Physostigmine

77.

As an antidote, repeat dosing of physostigmine was used, including total doses of, for example, 32-230 mg over up to a three-day period. Ketchum, J.S., CDRL Technical Memorandum 20-29: The Human Assessment of BZ (U), August 1963 (hereinafter "CDRL 20-29"), VVA024391 at 24438, 24460. When physostigmine is administered to combat the effects of an AChE inhibitor or anticholinergic agent, its immediate toxicity may be masked by the other agent.

78. *NRC Report Vol. 1* at E4; Physostigmine is currently approved by FDA for use in treating acute cholinergic toxicity, and it is not intended to be administered alone. There can be significant differences in the potential for harmful effects depending on whether physostigmine is administered alone or as a treatment following anticholinergic exposure. Ketchum, J.S. and F.R. Sidell, "Incapacitating Agents," in Medical Aspects of Chemical and Biological Warfare, *supra*, at VET004_000496. Ketchum and Sidell noted that while intramuscular doses of 4 mg are well tolerated when given as an anticholinergic antagonist, doses of as little as 2 to 3 mg alone cause symptoms of cholinergic intoxication. *Id*. Indeed, as discussed in detail above, physostigmine induces its own range of toxic effects. Edgewood Arsenal researchers observed that rapid intravenous dosing of physostigmine can lead to cardiac arrhythmias or even cardiac arrest. *Id.*

G. Government Studies of Long-Term Effects

79. There have been several government-sponsored studies of Edgewood Arsenal test subjects in an effort to assess long-term health sequelae from participation in the experiments. Two National Research Council studies and one by the Institute of Medicine focused on AChE inhibitors. While these studies largely concluded that there was insufficient evidence to prove the existence of long-term effects, in my view, the studies were statistically underpowered to detect anything but very large changes in risk. I have been informed that a detailed review of these studies is being provided by Daniel Ford, M.D., in a separate report, which I have not yet received or reviewed, and I may testify concerning Dr. Ford's opinions. Below I discuss my own observations of three of the studies with respect to the acetylcholinesterase inhibitors.

1. 1982 National Research Council Study on Long-Term Health Effects and Mortality

80. In a 1982 publication, the National Research Council Panel on Anticholinesterase Chemicals reported on their review of long-term effects and mortality in the Edgewood test subjects. *NRC Report Vol. 1* at x-xi. The morbidity analyses were derived from data in the records of Edgewood test subjects and the Council noted that the case summaries were merely

"brief and anecdotal," lacked an assessment of neurologic or psychologic examinations, and importantly provided none of the critical follow-up information that would be needed to assess long-term health consequences in this group. *NRC Report Vol. 1* at 29-30. The panel did acknowledge that the scientific literature provides at least some support for the idea that long lasting changes in EEG function, affect, sensation, memory, sleep patterns, and delayed central and peripheral neuropathic effects can occur from single exposures to OP agents. *Id.* at 30. As a result, the panel recommended follow-up studies with the test subjects specifically to consider the increased risk of these persistent changes. *Id.* at 30-33.

81. For the mortality analysis, the Council found that, at the time of review, there had been 222 reported deaths. *NRC Report Vol. 1* at 77. The report provides results in the form of standardized mortality ratios (SMR). The SMR is a ratio between the observed number of deaths in a study population and the number of deaths that would be expected, based on the age- and sex-specific rates in a standard population and the age and sex distribution of the study population. If the ratio of observed to expected deaths is greater than 1.0, there is said to be "excess deaths" in the study population.

82. Overall, the NRC study reports an overall SMR for the exposed service members of 0.81, an SMR of 0.72 for subjects exposed only to anticholinesterase agents, and an SMR of 0.67 for test subjects who were exposed to anticholinesterase agents as well as other test agents. *Id.* at 78, 86.[5] However, the study acknowledges the lower death rate for test subjects is likely due to the screening process the subjects went through to enter the military and the testing program at Edgewood, otherwise known as the "Healthy Soldier Effect." *Id.* at 78. In addition, the report noted that service members were exposed to more than one agent, which complicated the analysis for individual test compounds. *Id.* Even though the total deaths were less than

[5] The SMR data was updated by the NRC in a 1985 report to show SMRs of 0.69 (anticholinesterase exposure only) and 0.73 (anticholinesterase and other exposures), but the panel's conclusions were unchanged. "Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents," Vol. 3, Final Report, Current Health Status of Test Subjects, National Research Council, National Academy Press, Washington, D.C., 1985 ("*NRC Report Vol. 3"*) at 75, 78, VET013-005082, 5085.

expected, the study found that more deaths than expected were caused by leukemia and aleukemia, and half of these deaths were in service members who had been exposed to anticholinesterase agents in addition to other test agents. *Id.* at 80, 83.

83. As with the morbidity analysis, the primary limitation of this study is the small number of service members in the cohort, which renders the study underpowered to detect anything but very large statistically significant differences. As the report states, the study was "incapable of demonstrating risks of dying increased less than three- or four-fold." *Id.* at 80. Thus, it is statistically impossible for these mortality statistics to determine conclusively that there does or does not exist an increased mortality risk in the service members who were exposed to anticholinesterase agents at Edgewood Arsenal.

2. 1985 National Research Council Study on Long-Term Health Effects

84. To further assess morbidity in the Edgewood test subjects, the NRC panel solicited feedback from the test subjects themselves on long-term health effects, including cancer and adverse mental, neurologic, hepatic, and reproductive effects. "Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents," Vol. 3, Final Report, Current Health Status of Test Subjects, National Research Council, National Academy Press, Washington, D.C., 1985 ("*NRC Report Vol. 3"*) at "Executive Summary," VET013-005008-5009. While these analyses led the panel to conclude that subjects exposed to anticholinesterase chemicals did not differ significantly from controls in terms of these adverse effects, the panel acknowledged a possible increased risk of malignant neoplasms in these subjects. *Id.* at VET-013-005010. As with the earlier report, however, the panel cautioned that the study could only reveal "large effects" across the population. *Id.* at VET013-005010, 5016-5017. Further, the panel noted that the large standard error in the analysis, the lack of suitable control groups, the complicating factor of exposures to multiple agents, and the self-reporting aspect of the questionnaire-based study "would tend to obscure small differences." *Id.* at VET013-005010; *see also, Id.* at VET013-005035 ("Because of the shortcomings in test design, this evaluation is not likely or even intended to reveal minor health deficiencies that might have resulted from the test experience. Only major problems that occur in a large number of men are likely to be uncovered."). There

could be additional test bias arising from the fact that the sample necessarily excluded test subjects who could not be located or did not return questionnaires. *Id.* at VET013-005013-14. The panel also pointed out the potential for selection bias or "Healthy Soldier Effect" and the fact that healthier test subjects were used in active substance tests rather than placebo or equipment tests. *Id.*

85. For the subjects exposed to anticholinesterase chemicals, the panel acknowledged that while the primary health concerns were "subtle changes in EEG, sleep pattern, and behavior—such as increased irritability, inability to concentrate and depression[,]" persistent changes of these types would be difficult to detect. *Id.* at 27, VET013-005037. Nevertheless, the hospital admission rates for test subjects exposed to anticholinesterases were elevated relative to at least one of the comparator groups for mental disorders (*e.g.*, dementia, psychosis, schizophrenia, alcoholism, affective disorders, or personality disorders) and diseases of the nervous system and sense organs (*e.g.*, ataxia, multiple sclerosis, migraine, or nerve disorders). *Id.* at VET013-005025-26, 5058-59.

3. 2003 Institute of Medicine Follow-Up Study

86. In 2003, the Institute of Medicine reported the results of a telephone survey of 4,022 Edgewood test subjects. Page, W.F., "Long-Term Health Effects of Exposure to Sarin and Other Anticholinesterase Chemical Warfare Agents," *Military Medicine* 2003, 168(3), 239-245, VET001_015712-718. The methods used in the Page study were largely analogous to those used in the 1985 NRC report. *Id.* at VET001_015713. The study focused on particular long-term effects including sleep disorders, anxiety, depression, neurological deficits, peripheral nerve disease, and vestibular dysfunction, as "[o]ne would expect that these neurological and psychoneurological deficits would be more prevalent in the group…exposed to anticholinesterase agents." *Id.* at VET001_015712.

87. The Page study was subject to the same underlying problems as the previous studies, namely a small group size, lack of suitable controls, and insufficient statistical power to detect increases in risk. Nevertheless, the study did report that subjects exposed to AChE inhibitors had statistically more sleep disturbance problems, an effect that "is consistent with

reports of effects attributable to OP exposure[,]" and higher (although not statistically significant) risks for neurological and psychological health effects than the control groups. *Id.* at VET001_015717.

H. Summary

88. The weight of the scientific evidence demonstrates that exposure to AChE inhibitors such as the nerve agents, such as sarin, VX, soman, and tabun, and carbamates, such as physostigmine increases the risks of a wide range of long-term, deleterious health effects that persist well beyond the time of exposure. As discussed above, AChE inhibitors exert toxicity primarily through inhibition of AChE; thus, the risks of long-term health effects are increased in test subjects who demonstrated acute toxic effects. CWA Experiments at VET001_015680. Many of the subjects dosed with AChE inhibitors were exposed at levels that are likely to induce acute symptoms of cholinergic toxicity. However, because these agents have other modes of action, the increased risks of long-term health effects are not limited to situations in which acute toxicity is observed. In addition, simply participating in the testing program can increase the risk of PTSD and other psychological impacts, irrespective of dose received. Finally, repeat dosing regimens and regimens that involved exposure to multiple agents over a short period of time are likely to further increase the risk of potential negative long-term health effects.

89. Based on the scientific evidence, in my opinion, test subjects who were given even a single dose of an AChE inhibitor are at an increased risk of long-term physiological, behavioral, sleep, neurocognitive, neuropathic, and psychiatric changes. These long-term health effects include, but are not limited to: psychological effects, anxiety, depression, irritability, confusion, and difficulty concentating; deficits in affect, cognition, emotion, memory, problem-solving skills, intellectual ability, abstract thinking ability, and alertness; EEG abnormalities, sleep disturbances, insomnia, and narcolepsy; cardiac dysfunction; neuropathy, tremors, pain, weight loss, tingling in the extremeties, ataxia, muscle atrophy or necrosis, muscle stiffness, and muscle spasticity; fatigue; headache; visual disturbances; cancer; reproductive and birth defects; symptoms of PTSD; and effects on psychomotor performance, including deficits in motor speed, coordination, and visuospatial memory.

VII. CHOLINESTERASE REACTIVATORS

A. Military Interest in Cholinesterase Reactivators

90. Once acetylcholinesterase inhibitors were recognized as agents of chemical warfare, scientists began looking for treatments for exposure to these agents. While anticholinergic compounds, such as atropine, antagonize the muscarinic effects of the AChE inhibitors, they fail to ameliorate the nicotinic effects. *Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents*, Vol. 2 (Cholinesterase Reactivators, Psychochemicals, and Irritants and Vesicants), National Academy Press, 1984 (hereinafter "*NRC Report Vol. 2*"), at 3. The oximes pralidoxime chloride (2-PAM), pralidoxime mesylate (P2S), and trimedoxime (TMB-4) exhibit an antidotal effect primarily by hydrolyzing the inhibitor-enzyme complex to regenerate active AChE. *Id.* at 3-4, 11. 2-PAM is approved by the FDA for the treatment of OP pesticide and nerve agent poisoning. Label for PROTOPAM Chloride, at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/014134s022lbl.pdf. Because of the complementarity of receptor effects with atropine, a combination therapy with atropine and 2-PAM is a preferred treatment for OP poisoning. *Id.* at 4. However, as discussed above, these agents are ineffective as treatments for OP exposure once the inhibitor-enzyme complex has "aged" as the complex is no longer susceptible to hydrolysis. *NRC Vol. 1* at 11-12.

B. Mechanism of Action

91. The most well-characterized mechanism of action of the cholinesterase reactivators is regeneration of active AChE in the event of OP poisoning. However, as with the AChE inhibitors, these agents can impact the cholinergic system and other neurological pathways in ways that can lead to adverse acute and chronic adverse health effects. For example, cholinesterase reactivators are known to function as AChE inhibitors, in which case, exposures may increase the risk of any of the long-term sequelae discussed above in Section VI. *NRC Report Vol. 2* at 12-13, 26-28. In addition, the nucleophilic reaction of the oxime antidote with the AChE inhibitor-enzyme complex may produce another organophosphorus compound with potent AChE inhibition properties. *NRC Report Vol. 2* at 13, 15. The reactivators are also thought to affect acetylcholine release in peripheral and central cholinergic synapses,

allosterically modulate synaptic muscarinic receptors, alter nicotinic receptor-associated ion channels, stimulate release of norepinephrine, stimulate alpha- and beta-adrenergic receptors, inhibit the enzyme ATPase, and affect calcium mobility and metabolism. *NRC Report Vol. 2* at 12-13, 25-28; Bartosova, L. *et al.*, "The Acute Toxicity of Acetylcholinesterase Reactivators in Mice in Relation to Their Structure," *Neurotox. Res.* 2006, 9(4), 291-296. 2-PAM has also been shown to have a damaging effect on the integrity of cell membranes. *NRC Report Vol. 2* at 279. As with the AChE inhibitors discussed above, the actions of these agents are complex and diverse.

92. In general, the cholinesterase reactivators exhibit relatively poor pharmacokinetic properties, including rapid metabolic clearance and slow absorption, and some have a low instrinsic ability to cross the blood-brain barrier. *NRC Report Vol. 2* at 16-17. Because of these limitations, antidotal therapy generally requires repeated dosing or a continuous intravenous infusion or large quantities, and/or adjunct therapy with other agents. *NRC Report Vol. 2* at 16. Despite these limitations, however, treatment with these compounds does generate pronounced improvement in the acute effects of OP nerve agent poisoning. *NRC Report Vol. 2* at 16-17. It is clear, then, that the compounds are able to reach the peripheral and central nervous systems in sufficient quantities to exert their antidotal effects.

C. Acute Clinical Effects from Exposure to Cholinesterase Reactivators

93. Acute toxicity of the cholinesterase reactivators such as 2-PAM and P2S manifests in a diverse range of symptoms, including a bitter taste in the mouth, dizziness, double vision, eye discomfort, blurred vision with impaired accommodation, muscle weakness, nausea, vomiting, muscle pain, hypertension, tachycardia, and gastrointestinal distress including abdominal cramps and diarrhea. *NRC Report Vol. 2* at 18-28, 32, 34, 278. When administered as an antidote, cholinesterase reactivators can cause temporary worsening of cholinergic effects of AChE inhibitor poisoning (including cardiac arrest, laryngospasm, and muscle rigidity). *NRC Report Vol. 2* at 28-29. Signs of severe intoxication include strange or confused behavior, severe difficulty breathing or respiratory secretions, severe muscular twitching, muscle weakness, and involuntary urination or defecation. PROTOPAM label at 9. Generally, these acute effects are

transient but they can last at least a few hours after administration. *NRC Report Vol. 2* at 18. From these observations, it is clear that the biochemical effects of these agents are complex.

D. Long-Term Health Effects of Acute or Sub-Chronic Exposure to Cholinesterase Reactivators

94. As indicated in the National Research Council report, studies on the long-term effects of acute or chronic dosing with cholinesterase reactivators are generally lacking in the scientific literature. *NRC Report Vol. 2* at 30-31. As the cholinesterase reactivators are typically administered alone or with atropine following exposure to OP nerve agents or pesticides, there is limited data available to evaluate the effects of the cholinesterase reactivators alone. Nevertheless, as discussed above, these agents appear to interfere with a wide array of neurological processes, and exposure to these agents could reasonably be expected to increase the risks of long-term psychological, neurobehavioral, or neuropathic effects. In terms of peripheral effects, evidence of hepatic injury from chronic exposure to 2-PAM has been reported. *NRC Report Vol. 2* at 18, 25. Acute oxime exposure has also been linked to effects on renal tubules (excretion of the large antidotal doses of these agents occurs via renal tubular secretion), and muscle necrosis following intramuscular injection. *Id.* at 31; Label for PROTOPAM Chloride, *supra*, at 3). Possible mutagenic or carcinogenic effects of these compounds have not been well-characterized, but likewise have not been affirmatively ruled out. *NRC Report Vol. 2* at 29. Effects on a broad array of cardiac functions have been observed, but the implications of these data for long-term health effects are unknown. *Id.* at 26-27. I agree with the conclusions of the National Research Council panel that preliminary toxicity findings in the literature require further study in order to determine the potential of these substances to induce long-term health effects. *NRC Report Vol. 2* at 31. In my view, based on the current state of knowledge regarding the breadth of biochemical effects of the cholinesterase reactivators, acute or short-term repeated exposure to cholinesterase reactivators is likely to increase the risk of adverse long-term health effects. These effects may include, but are not limited to, the effects described above for the AChE inhibitors, as well as cardiac, renal, and hepatic changes, mutagenicity and carcinogenicity,

and muscle necrosis. Certainly, an increase in risk of this array of health effects cannot be ruled out based on the current scientific understanding of these agents.

E. Testing of Cholinesterase Reactivators at Edgewood Arsenal

95. During testing at Edgewood Arsenal, the antidotal effectiveness of the oxime agents was found to vary across species and OP agents; thus, *in vitro* or *in vivo* animal studies were of limited value. *NRC Report Vol. 2* at 4-6. The cholinesterase reactivators were therefore evaluated in military subjects between 1958 and 1975, both as single agents and in combination with a range of other substances, including VX, soman, atropine, physostigmine, and benzactyzine.[6] *Id.*

In some studies, these agents were administered before or after administration of an OP nerve agent. *NRC Report Vol. 2* at 31, 34.

[6] At least two Edgewood Arsenal test subjects had severe acute reactions to the cholinesterase reactivators. In one case, a subject who received 2 g of P2S and 1 g of TMB-4, followed by 1.5 µg of soman, became anxious, restless, and agitated 12 hours after exposure and had to be transferred to Walter Reed Hospital for treatment. *NRC Report Vol. 2* at 36. A second suffered a grand mal seizure three hours after receiving the third of three doses of 2-PAM administered over an eight-day period. *NRC Report Vol. 2* at 36.

96. A large number of the Edgewood Arsenal test subjects received doses of 2-PAM and P2S in the absence of any OP poisoning, or in combination with anticholinergics, AChE inhibitors, and/or psychochemicals. The majority of the scientific understanding of the toxicity of the cholinesterase reactivators in humans comes from their use as antidotes for OP poisoning. Using these agents without OP toxins, or in conjunction with non-OP agents that act by different neurological mechanisms, may exacerbate their potential for inducing long-term health problems. Use of cholinesterase reactivators like 2-PAM as antidotes for carbamate AChE inhibitor exposure (such as physostigmine) is contraindicated as 2-PAM may exacerbate toxicity of the AChE inhibitor. PROTOM label at 4.

97. As mentioned above, cholinesterase reactivators were primarily used in test subjects for treatment of OP poisoning, with or without atropine. However, while cholinesterase reactivators may be beneficial in reducing acute symptoms of OP toxicity, the acute symptoms of the OP agent and/or atropine may mask toxic effects of the reactivators. PROTOPAM label at 7. In addition, these antidotal agents do not affect other mechanisms of OP agent activity, such as NTE inhibition, that are thought to be the primary cause of the long-term health effects of AChE inhibitors. Combination of the reactivators with anticholinergics such as atropine may cause an enhanced reaction to the anticholinergics. PROTOPAM label, at 5, 7.

98. In the absence of robust studies demonstrating a lack of long-term health effects from acute or sub-chronic exposure to cholinesterase reactivators, alone or in conjunction with, it cannot be concluded that test subjects would have no health effects from exposure to cholinesterase reactivators. Furthermore, as discussed above, long-term psychiatric effects, including PTSD, may result simply from participating as a test subject in military chemical warfare research.

F. Government Studies of Long-Term Effects

99. The two National Research Council studies discussed above in Section VI(G) also addressed the issue of whether there were indications of long-term health effects in the Edgewood

Arsenal test subjects exposed to cholinesterase reactivators. In the 1982 report, the National Research Council determined an SMR of 1.20 for test subjects exposed to these agents alone, indicating a 20% increased incidence of death among these veterans relative to the expected level. *NRC Report Vol. 1* at 79, 83. When the study was updated in 1985, the SMR figure for this group jumped to 1.47, which represents a large substantive increase in mortality. *NRC Report Vol. 3* at 78. These reviews also found an increased incidence of leukemia among the deaths in the test group exposed to cholinesterase reactivators in combination with other agents. *NRC Report Vol. 1* at 80, 83; *NRC Report Vol. 3* at 78. However, for the reasons discussed above, these studies were underpowered to detect anything but a very large increase in risk of long-term health effects, meaning that many other less dramatic adverse health effects would have been missed.

G. Summary

100. In my opinion, and for the reasons described above, there is sufficient evidence to indicate that military service members who were exposed to acute or sub-chronic doses of cholinesterase reactivators such as 2-PAM, P2S, and TMB-4, either alone or in combination with OP nerve agents, anticholinergics, or other biologically active substances, are subject to an increased risk of long-term adverse health effects. These effects include but are not limited to the symptoms and disorders listed above for exposure to AChE inhibitors, as well as hepatic dysfunction, kidney problems, and muscle necrosis.

VIII. ANTICHOLINERGIC COMPOUNDS

A. Military Interest in Anticholinergic Compounds

101. Interest in the potential military use of anticholinergic compounds as incapacitating agents arose along with that for the anticholinesterase agents in the late 1940s. *NRC Report Vol. 1* at 1. This class of compounds includes the tropane alkaloids atropine and scopolamine and the synthetic glycolates such as BZ. These agents are considered to be incapacitating agents because their acute effects include delirium, including confusion, hallucinations, and disorganized speech and behavior. FM 3-11.9 at VET013-004755-56. The anticholinergics were seen as preferred incapacitating agents over the anticholinesterase agents

because of their potency and higher safety margin (ratio of lethal dose to incapacitating dose is relatively large). *Id.* at VET013-004756.

B. Mechanisms of Action

102. The majority of anticholinergic agents work by inhibiting the ability of acetylcholine ("ACh") to bind to its muscarinic receptors. As discussed above, muscarinic receptors are distributed in the parasympathetic nervous system, and are therefore involved with regulation of processes such as heart rate, bronchoconstriction, vasodilation, intestinal motility, gland secretion, and bladder contraction. However, as with the AChE inhibitors, the anticholinergics are neurologically active compounds that are likely to have actions that go beyond their strict antimuscarinic effects, and such mechanisms may not be well-characterized.

103. The anticholinergics are generally well-absorbed when administered by oral, dermal, intramuscular, or intravenous routes, or by inhalation. Ketchum, J.S. and H. Salem, "Incapacitating Agents," in Medical Aspects of Chemical Warfare, Chapter 12, PLTF010456-10485, at PLTF010467. Atropine and scopolamine can cross the blood-brain barrier, and the synthetic glycolates were designed to have this characteristic. Ketchum, "Incapacitating Agents," Medical Aspects of Chemical Warfare, at PLTF010467; *NRC Report Vol. 1* at 54. Indeed, the centrally active agents BZ and EA 3443 were a focus of the testing at Edgewood. *Id.* at 54, 55. These compounds are widely distributed in the periphery and in various brain regions, including, for example, the motor cortex, sensory cortex, thalamus, and hypothalamus. *Id.* at 55-56. Compounds such as BZ have been shown to have strong affinity for brain mitochondria. *Id.* at 55-56. In addition, anticholinergic agents that produce particularly long durations of action may bind irreversibly to brain receptors. *Id.* at 57.

C. Acute Clinical Effects from Exposure to Anticholinergic Compounds

104. As with the acetylcholinesterase inhibitors, the acute clinical effects of anticholinergic agents across the class are qualitatively similar, while quantitative differences in severity and range of symptoms, time of onset, and duration of effect may vary due to the particular agent, route of administration, and dose. *Id.* at 51. Atropine is considered to be the prototypical anticholinergic agent, and its effects are representative of this class of agents.

105. Acute effects of exposure to anticholinergic compounds in the periphery include inhibition of salivary and bronchial secretions (dry mouth), mydriasis (pupil dilation), reduced accommodation of the eye (difficulty focusing), increased body temperature (and reduced sweating), peripheral vasodilation, increased heart rate and blood pressure, inhibition of urination, and decreases in intestinal tone and motility. *NRC Report, Vol. 1* at 52, 53; CDRL 20-29 at VVA 024339. In the central nervous system, acute effects include moderate sedation, diminished alertness and mental slowing, dulling of affect, decreased spontaneity, lowered interest in work and recreational activity, increased respiratory rate, restlessness, irritability, disorientation, memory impairment, ataxia (muscular incoordination), hallucinations, and delirium. *NRC Report, Vol. 1* at 52-53; CDRL 20-29 at VVA 024339. At higher doses, the effects are intensified, and significant effects on motor coordination, attentiveness, short term memory, confusion are observed. CDRL 20-29 at VVA 024339. These stimulatory effects are generally followed by a depressive episode, which may include coma with potentially fatal outcomes. *NRC Report, Vol. 1* at 52.

106. The estimated safety margins for the anticholinergics in humans, namely the ratio of LD_{50} to ID_{50} (dose needed to incapacitate 50% of treated subjects), range from about 40 for BZ to about 100 for scopolamine. *NRC Report Vol. 1* at 60; Ketchum and Sidell, "Incapacitating Agents," VET004_000482 at 491. Estimated LD_{50} values in this class range from about 60 µg/kg for EA3834, to about 200 µg/kg for BZ, to about 5-10 mg/kg for atropine. *NRC Report Vol. 1* at 60; Ketchum and Sidell, "Incapacitating Agents," at VET004_000491. The ID_{50} values range from about 1.2 µg/kg for EA3834, to approximately 5-8 µg/kg for BZ (intravenous, intramuscular, or oral exposure), and 140 µg/kg for atropine. *NRC Report Vol. 1* at 60; Ketchum and Sidell, "Incapacitating Agents," at VET004_000491-492. The minimally effective dose of BZ to exhibit mild cognitive impairment in 50% of an exposed population is only 2.5 µg/kg. Ketchum and Sidell, "Incapacitating Agents," at VET004_000491-492. However, administration of these agents under stress or heat conditions can significantly lower the doses necessary to produce such effects, as indicated by the fact that "fatal hyperthermia or heatstroke could occur at

doses very close to the ID_{50} for BZ and not more than 2 or 3 times the ID_{50} for EA 3834." *NRC Report Vol. 1* at 61.

D. Long-Term Health Effects of Acute or Sub-Chronic Exposure to Anticholinergic Compounds

107. Reports of delayed or long-term adverse health effects from exposure to anticholinergic agents are not as prevalent as those for AChE inhibitor exposure, in part because large exposed study populations (farm workers and victims of terrorist attacks) have not been available. Nevertheless, there have been indications that long-term sequelae can result from exposure to anticholinergics.

108. Several reports have documented persistent neurological impacts following anticholinergic exposure, such as flashbacks and deficits in cognitive function. *Id.* at 66. There have also been indications of possible kidney and liver effects, including glomerulitis, renal toxicity, and hematuria. *Id.* at 59, 65-67. Studies with BZ have indicated that it is a weak mutagen in yeast cells and in bone marrow cell chromosomes. *Id.* at 60. Such results could indicate an increased risk of cancer. There is also an indication in the literature that the interaction of BZ with certain brain receptors could be irreversible. *Id.* at 57. As with the other classes of compounds, exposure to these agents can increase the risk of PTSD and related psychological impacts, regardless of the dose received.

109. AChE inhibitors such as physostigmine are often used for treating the acute effects of anticholinergic exposure. *Id.* at 54. AChE inhibitors do not function as a mechanistic antidote, however, as they increase the ACh concentration in the synapse but have no direct effect on muscarinic receptor blockade or any other modes of action at play.

110. Some of the symptoms that have been noted as potential long-term adverse effects of anticholinergic exposure are consistent with the long-term sequelae linked to exposure to AChE inhibitors. This is perhaps unsurprising given that both classes of compounds interact primarily with the same neurological systems. Therefore, it is reasonable to consider that exposure to the anticholinergics, with or without concomitant exposure to an AChE inhibitor, can

increase the risk of a number of long-term adverse health effects, including the symptoms and disorders mentioned above for the AChE inhibitors.

E. Testing of Anticholinergic Compounds at Edgewood Arsenal

111. The anticholinergic compounds were among the most frequently tested at Edgewood Arsenal, with at least 1800 test subjects exposed to 24 anticholinergic compounds. *Id.*, at x.

112. Dosing ranges that were used in human experiments for each of these exemplary agents are shown in the table below:

Agent	Exemplary Doses (mode of administration)
Atropine	
BZ	
Scopolamine	
EA3443	
EA3580	
EA3834	

NRC Report Vol. 1 at 71; Sidell, F.R., "A Summary of the Investigations in Man with BZ Conducted by the U.S. Army, 1960-69" (hereinafter "Sidell/BZ"), JK15 0022492 at 22515. A number of test subjects were exposed to multiple doses of these agents, for example, in daily repeat doses, or by different modes of administration a number of

days apart.[7]

In my view, the doses of anticholinergics listed above would be likely to induce acute toxic symptoms in test subjects. For example, as noted above, in the vast majority of cases, the doses of BZ used in these tests exceeded the levels determined to be the minimum effective dose. I have also received a summary of selected dose and exposure pathway data which I understand were drawn from three sources (the Chem-Bio database, and Dr. Ketchum's book), sources which in general show the wide ranges of doses.

113. A more detailed discussion of exemplary testing done with each of the more commonly tested agents is presented below.

1. BZ

114. A broad range of human studies were done with BZ between 1960 and 1969. *NRC Report Vol. 1* at 2; Sidell/BZ at JK15 0022515-22519. Human experiments were intended to determine equipotent doses by different modes of administration, effects on performance of military tasks, whether effects would be cumulative on daily dosing, or whether the compound caused sensitization. Sidell/BZ at JK15 0022499. BZ was also tested on human subjects in field tests and under heat stress conditions. *Id.* at JK15 22505.

115. BZ is one of the longest-acting of the anticholinergics; indeed, on acute dosing, pharmacologic effects were evident in human subjects even a week after exposure. *NRC Report Vol. 1* at 57. Cumulative toxic effects were observed in subjects on repeat dosing of BZ. Sidell/BZ at JK15 0022518. I also understand that Dr. James Ketchum, a doctor who

[7] Exemplary dosing regimens for BZ include:

administered testing at Edgewood Arsenal, testified that BZ was rejected by the Hoffman LaRoche pharmaceutical firm because of undesired side effects, including confusion, hallucinations, and difficulty thinking. Ketchum Deposition Transcript at 310:21–311:6.

2. Synthetic BZ Analogs

116. A number of synthetic BZ analogs were tested on human subjects in the testing program, including EA3443, EA3580, EA3834, and EA3167. All of these agents produced the same constellation of acute effects as BZ, but differed in their time of onset and duration of action. *See, e.g.*, Ketchum, J.S. *et al.*, "The Human Assessment of EA 3443," Edgewood Arsenal Technical Report (EATR 4066), March 1967, JK01 0001965 at 1970. For example, the effects of EA3167 are particularly persistent. Following accidental exposure of a lab pharmacologist to EA3167, it took one year for recovery. September 25, 1981 Minutes of Second Meeting, Anticholinergic Panel at JK07 0011505.

117. Of consequence, urinary abnormalities in the form of microscopic pyuria were observed in two subjects who were exposed to EA3580. "EA 3580, Field Tests and Urinary Abnormalities," 6 November 1967, and "Field Performance Tests Using EA3580," 19 September 1969, at JK15 0020990-94. Despite these problems, and the fact that a number of the research physicians expressed concern about the safety of the drug, the research group decided to continue testing. *Id.* With respect to EA3834, the clinical research team noted concern about potential nephrotoxicity from this compound based on elevated blood urea nitrogen values and hematuria in animal studies and the development of persistent hematuria and transient RBC cylindruria in one test subject. Memoranda, "Interim Report EA 3834," 3 November 1968, "Use of EA 3834 in Human Volunteers," 29 January 1969, JK15 0020955-20962.

3. Atropine and Scopolamine

118.

Andrews, P. *et al.*, "Evaluation of Atropinization by Various Routes in Humans," Contract Report, MLCR No. 59, July 1955, at JK15 0021612-13.

119. Studies with these agents in test subjects produced the typical acute effects of this class of compounds, including tachycardia, dry mouth, somnolescence, restlessness, ataxia, incoordination, hyperreflexia, hyperthermia, hypertension, loss of awareness, attention deficits, and difficulty speaking. Ketchum, J.S. *et al.*, "Atropine, Scopolamine, and Ditran: Comparative Pharmacology and Antagonists in Man," Edgewood Arsenal Technical Report (EATR) 4761, August 1973, JK02 0004138 at 4146-4150.

F. Government Studies of Long-Term Effects

120. The National Research Council studies discussed above in Section VI(G) assessed the long-term health effects of exposure to anticholinergic compounds in Edgewood Arsenal test subjects. In the 1982 report, the National Research Council determined an SMR of 1.06 for test subjects exposed to these agents alone, indicating a 6% increased incidence of death among these veterans relative to the expected level. *NRC Report Vol. 1* at 83. As discussed above, these studies were underpowered to detect anything but very large changes, meaning any adverse health effects of low incidence would have been missed. The National Research Council concluded that while "[n]o firm evidence has been seen that any of the anticholinergic test compounds surveyed produced long-range adverse human health effects in the doses used at Edgewood Arsenal[,] [m]ore intensive study is *required* to confirm this conclusion." *NRC Report, Vol. 1*, at xi (emphasis added).

G. Summary

121. In my opinion, and for the reasons described above, there is sufficient evidence to indicate that military service members who were exposed to acute or sub-chronic doses of anticholinergics, either alone or in combination with AChE inhibitors or other biologically active substances, are subject to an increased risk of long-term adverse health effects. These effects include but are not limited to the symptoms and disorders listed above for exposure to AChE inhibitors, as well as kidney or urinary problems.

IX. OUTREACH LETTER AND RELATED MATERIALS

122. I have been asked to review Department of Veterans Affairs Outreach Letter and associated Fact Sheet and Frequently Asked Questions attachments for potential medical and scientific inaccuracies. VET001_015129-130; VET001_015131-132; VET001_015133-134.

123. I have been informed and understand that the Outreach Letter is a generic form letter that was sent to a number of test subjects along with the Fact Sheet and Frequently Asked Questions sheet. The letter does not give any particular agent or exposure information for the recipient of the letter. VET001_015129. Furthermore, the letter indicates that VA will notify the service member of any "long-term health effects associated with in-service exposure to chemical and biological agents" if "the medical community identifies" such effects. VET001_015130. As discussed above, however, while the specific studies of veteran test subjects were underpowered to detect long-term health changes, the scientific literature supports the conclusion that exposure to anticholinesterases, cholinesterase reactivators, and anticholinergics increases the risk of a range of long-term health effects. These details are not included in the letter.

124. The Department of Defense Fact Sheet makes several inaccurate statements. First, the Sheet states that the studies performed between 1982 and 1985 by the National Research Council "did not detect any significant long-term health effects in Edgewood Arsenal volunteers." VET001_015131. As discussed above, the studies were underpowered to detect anything other than very large statistical increases in the risk of health effects, regardless of the significance of the effect. Thus, the studies missed adverse health effects that were not as prevalent. Even so, the studies did reveal a small increase in certain health impacts, and advocated further studies due to indications from the scientific literature that long-term health effects could arise from acute exposures to the test agents.

125. Second, the Fact Sheet states that Edgewood Arsenal tests included "classified medical studies involving nerve agents, nerve agent treatments (antidotes), psychochemicals (hallucinogenic drugs), irritants, and blistering agents." VET001_015131. It does not list incapacitating anticholinergic agents. Further, the statement appears to characterize the cholinesterase reactivators and anticholinergics as "nerve agent treatments (antidotes)," when

these agents, particularly the anticholinergics, were tested as incapacitating agents in their own right.

126. In two different places in the Fact Sheet, the program is mentioned as having evaluated "low-dose exposures to chemical agents." VET001_15131. In my view, this statement is inaccurate, as a "low dose" is a term of medical consequence that refers to a dose that is below that needed to produce any undue effects or toxicity. Yet the majority of test subjects were exposed to doses sufficient to produce immediate symptomatic responses, and therefore the doses cannot accurately be characterized as "low." In my opinion, moreover, based on the scientific literature on these biologically complex agents, it is not possible to rule out the possibility of adverse health effects even at doses below those necessary to produce signs of acute toxicity.

127. The Frequently Asked Questions attachment ("FAQ") includes additional inaccuracies. In Table 1, the FAQ mentions that approximately 30% of volunteer hours were spent testing "Incapacitating compounds (i.e. vomiting agent)." VET001_015134. In my medical opinion, the incapacitating agents tested at Edgewood include the anticholinesterase and anticholinergic classes of compounds, which induce much more serious effects than emesis.

128. In conclusion, in my view, a number of statements in the Outreach Letter and related documents are scientifically and medically inaccurate.

X. PROPER MEDICAL FOLLOW-UP

129. In order for testing program participants to obtain adequate ongoing health care and monitoring, it is critically important that each participant is informed about what substance or substances he was exposed to, in what dose, through what route of administration, and under what conditions. In addition, each testing program participant should be informed about any observed acute effects he experienced, and about the state of the scientific understanding about possible long-term adverse health effects from exposure to those particular substances or from participation in the testing program. Having such information is necessary so the service member can communicate appropriately with his health care provider and make informed medical decisions that take the increased health risks into account.

130. In my view, because adverse health effects from exposure to the test agents may occur at a low frequency at any given time, the most effective way to evaluate the test subjects for long-term adverse health effects would be a comprehensive medical follow-up program. Ideally, this program would be run by the agencies involved in these testing programs, as those organizations have the most accurate information regarding the exposures received by the test subjects.

XI. CONCLUSION

131. In my opinion, the military service members who were exposed to anticholinesterases, cholinesterase reactivators, and/or anticholinergics during military chemical weapons test programs are at an increased risk for the long-term health effects I have discussed in this report. The scientific and medical literature supports the conclusion that subjects exposed to such agents, even with a single dose at levels below that necessary to cause significant immediate effects, are at an increased risk of developing the types of symptoms and disorders described above. Where affirmative scientific evidence is lacking or otherwise unconfirmed, the literature is insufficient to rule out the possibility of these increased health risks in the test subjects. Furthermore, mere participation in the chemical testing program would be expected to increase the risk that test subjects would develop PTSD and associated negative outcomes, irrespective of the substance or dose received.

Respectfully submitted,

Dated: August 7, 2012

Steven B. Bird, M.D.

EXHIBIT 1

July 2012

Steven B. Bird, M.D.

PERSONAL INFORMATION:

Address: Department of Emergency Medicine
Division of Toxicology
University of Massachusetts Medical School
55 Lake Avenue North
Worcester, MA. 01655 USA

Home:

Telephone:
FAX:
E-mail:

Date of birth:

Place of birth:

Marital status:

EDUCATION:

1987 – 1991	B.S. Biology, *cum laude* Yale University New Haven, Connecticut
1991 – 1995	M.D. - *Alpha Omega Alpha National Medical Honor Society* Northwestern University Chicago, Illinois

POST-GRADUATE TRAINING:

1995 – 1996	Resident in Surgery Naval Hospital San Diego San Diego, California
1996 – 1999	US Naval Flight Surgeon Marine Corps Air Station Futenma Okinawa, Japan
1999 – 2002	Resident in Emergency Medicine University of Massachusetts Medical School Worcester, Massachusetts
2001 – 2002	Chief Resident in Emergency Medicine University of Massachusetts Medical School Worcester, Massachusetts
2002 – 2004	Fellow in Toxicology University of Massachusetts Medical School

Worcester, Massachusetts

LICENSURE AND BOARD CERTIFICATION:

American Board of Emergency Medicine, 2003

American Board of Toxicology, 2004

Massachusetts Physician License

ACADEMIC APPOINTMENTS:

Jan 2010 – current	Associate Professor of Emergency Medicine Department of Emergency Medicine University of Massachusetts Medical School Worcester, Massachusetts
Sept 2004 – Jan 2010	Assistant Professor of Emergency Medicine Department of Emergency Medicine University of Massachusetts Medical School Worcester, Massachusetts
Aug 2002 – Aug 2004	Instructor of Emergency Medicine Department of Emergency Medicine University of Massachusetts Medical School Worcester, Massachusetts

HOSPITAL AND MEDICAL SCHOOL APPOINTMENTS:

3/2012-current	Vice Chair of Education, Department of Emergency Medicine, University of Massachusetts Medical School, Worcester, Massachusetts
3/2011-current	Program Director for Emergency Medicine Residency, University of Massachusetts Medical School, Worcester, Massachusetts
2002 - current	Attending Emergency Physician, University of Massachusetts Medical Center, Worcester, Massachusetts
2002 - current	Attending Emergency Physician, Marlborough Hospital, Marlborough, Massachusetts
2002 - current	Attending Emergency Physician, Clinton Hospital, Clinton, Massachusetts

MEMBERSHIPS AND SOCIETIES:

1998 - current	Society for Academic Emergency Medicine
1998 - current	American College of Emergency Physicians

2001 - current	American College of Medical Toxicology
2004 – current	Asia Pacific Association of Medical Toxicology

HONORS AND AWARDS:

2007	Young Investigator Award. From the Society for Academic Emergency Medicine
2002	Society for Academic Emergency Medicine Best Resident Basic Science Presentation. Annual meeting of SAEM, St. Louis, Missouri
2002	SAEM New England Regional Research Directors Excellence in Research Award
1999	Navy and Marine Corps Achievement Medal
1990	Yale University Richter Fellow

PROFESSIONAL ACTIVITIES:

Departmental/Institutional:

2011 – present	Umass Memorial Medical Center President-Elect of Medical Staff
2011 – present	UMass Memorial Medical Center Chair, Credentials Committee
2010 – present	UMass Memorial Medical Center Medical Staff Executive Committee
2006 – 2011	UMass Memorial Medical Center, Department of Emergency Medicine Physician Incentive Compensation Committee Chair
2004 – 2011	UMass Memorial Medical Center Moderate Sedation Committee
2003 – present	UMass Memorial Medical Center, Department of Emergency Medicine Research Committee
2002 – present	University of Massachusetts Medical School Emergency Medicine Residency Selection Committee

National:

2008 - present	Society for Academic Emergency Medicine Annual Meeting Program Committee
2004 – present	Society for Academic Emergency Medicine Grants Committee

2003 – 2010	American College of Emergency Physicians Scientific Review Committee
2003 – 2004	Society for Academic Emergency Medicine Research Committee

International:

2004 – present	Southeast Asia Toxicology Research Consortium

Scholarly:

2009 – present	Editorial Board member of *Academic Emergency Medicine*
2009 – present	Editorial Board member of *The Open Toxinology Journal*
2005 – 2011	Editorial Board member of *Journal of Medical Toxicology*
	Manuscript reviewer for *JAMA; Academic Emergency Medicine; Annals of Emergency Medicine; Pediatrics; Journal of Emergency Medicine; Journal of Medical Toxicology; Clinical Toxicology; The Open Toxinology Journal; PLoS One*

Invited Attendance:

Dec 2007	5th Asia Pacific Association of Medical Toxicology (APAMT) meeting, Bangkok, Thailand
Aug 2006	5th Congress of APAMT, Colombo, Sri Lanka
May 2004	8th International Symposium on Protection Against Chemical Warfare Agents, Munich, Germany

MENTORING

Successfully mentored junior faculty members in the Department of Emergency Medicine in writing and procuring K08 and K23 awards.

TEACHING RESPONSIBILITIES:

Grand Rounds

North Country Hospital: "Pattern Recognition in Adverse Drug Events" February 2011, Newport, Vermont

Washington University School of Medicine: ""Translational Research in Emergency" September 2010, St. Louis, Missouri

University of Massachusetts Medical School: "Translational Research in Emergency Medicine and Building an Academic Career" July 2009 Worcester, Massachusetts

Children's Hospital Boston - Pediatric Emergency Medicine and Massachusetts Poison Control Center; "Acetylcholinesterase Inhibitors" May 2008, Boston, Massachusetts

University of Massachusetts Medical School: "Translational Research in Emergency Medicine: from Benchtop to Sri Lanka" June 2007 Worcester, Massachusetts

University of Iowa, Department of Emergency Medicine. "Organophosphates and Chemical Nerve Agents." November 2005, Iowa City, Iowa

Invited Lectures
University of Iowa, Department of Emergency Medicine. "Antidepressant Poisoning." April 2006, Iowa City, Iowa

University of Iowa, Department of Emergency Medicine. "Pattern Recognition in Toxicology." April 2006, Iowa City, Iowa

Brigham and Women's Hospital, Division of Emergency Medicine: "Cardiovascular Poisonings" May 2006, Boston, Massachusetts

Center for Disease Control and Prevention. Agency for Toxic Substances and Disease Registry. "Agents of Opportunity: Toxic Gases"
March 2005, Hartford, Connecticut

Brigham and Women's Hospital, Division of Emergency Medicine: "Procedures in Toxicology" February 2005, Boston, Massachusetts

Baystate Medicine Center, Department of Emergency Medicine "Poison Control Center Functions" March 2004, Springfield, Massachusetts

Portsmouth Naval Medical Center: "Pattern Recognition in Toxicology"
March 2003, Portsmouth, Virginia

Harvard School of Public Health: "Neurotoxicology"
October 2003, Boston, Massachusetts

Classroom Lectures (selected)
University of Massachusetts Emergency Medicine Residency: "Bibliometrics: from Impact Factors to h-Indices" July 2012, Worcester, MA

University of Massachusetts Emergency Medicine Residency: "How to Give a Presentation"
Aug 2011, Worcester, MA

University of Massachusetts Emergency Medicine Residency: "Endocrine Emergencies"
Feb 2007, Worcester, MA

University of Massachusetts Emergency Medicine Residency: "Pattern Recognition in Toxicology"
July 2006, Worcester, MA

University of Massachusetts Emergency Medicine Residency: "Toxic Alcohols"
April 2004, Worcester, MA

University of Massachusetts Emergency Medicine Residency: "Central Venous Access"
August 2003, Worcester, MA

University of Massachusetts Emergency Medicine Residency: "Introduction to the Poisoned Patient"
July 2003, Worcester, MA

Massachusetts College of Pharmacy: "Summertime Poisonings"
July 2003, Worcester, MA

Massachusetts College of Pharmacy: "Introduction to the Poisoned Patient"

May 2003, Worcester, MA

Emergency Medical Services: "A Trip Through the Medicine Cabinet"
December 2002, Williamstown, MA

University of Massachusetts Emergency Medicine Residency: "Acetaminophen"
August 2002, Worcester, MA

University of Massachusetts Emergency Medicine Residency: "Anti-hypertensive Poisonings"
January 2002, Worcester, MA

Clinical Teaching and Supervision
Responsible for all aspects of training for 36 emergency medicine residents in a PGY1-3 program.

Oversees residents and medical students approximately 50 hours/month in the emergency department.

Oversees 3 medical toxicology fellows and one emergency medicine resident per month.

Participates in weekly toxicology conference for residents, fellows, and pharmacists.

PAPERS IN PEER-REVIEWED JOURNALS:

1. Dunn C, **Bird SB**, Gaspari R "Intralipid fat emulsion decreases respiratory failure in a rat model of parathion exposure." *Acad Emerg Med*. 2012;19(5):504-9.

2. Rosenbaum C, **Bird SB** "Non-muscarinic targets of organophosphorus pesticides." *J Med Toxicol* 2010; 6(4):408-12.

3. Jackson CJ, Scott C, Carville A, Mansfield K, Ollis DL, **Bird SB**. Pharmacokinetics of OpdA, an organophosphorus hydrolase, in the African green monkey. Biochem Pharmacol 2010;80:1075-9.

4. Gresham C, Rosenbaum C, Gaspari R, Jackson CJ, **Bird SB**. "Kinetics and efficacy of an organophosphorus hydrolase in a rodent model of methyl-parathion poisoning. *Acad Emerg Med* 2010; 17:736-740.

5. **Bird SB**, Dawson A, Ollis D. "Enzymes and bioscavengers for prophylaxis and treatment of organophosphate poisoning" *Front Biosci* 2010; S2:209-220.

6. Rosenbaum CR, Church R, **Bird SB**. "Timing and frequency of physostigmine redosing for antimuscarinic toxicity" *J Med Toxicol* Published online April 20, 2010. DOI 10.1007/s13181-010-0077-7

7. Weibrecht K, Dayno M, Darling C, **Bird SB**. ""Liver aminotransferases are elevated with rhabdomyolysis in the absence of liver injury" *J Med Toxicol.* Published online April 21, 2010. DOI 10.s131181-010-0075-9

8. **Bird S,** Sutherland T, Gresham C, Oakeshott J, Eddleston M. "OpdA, a Recombinant Bacterial Organophosphorus Hydrolase, Prevents Lethality in Rats After Poisoning with Highly Toxic Organophosphours Pesticides" Toxicol 2008;247: 88-92.

9. **Bird SB**. "Impact Factors, H Indices, and Citation Analyses in Toxicology Journals" J Med Toxicol 2008;4: 261-274.

10. **Bird S,** Sivilotti M. "Self-plagiarism, textual reuse, and the intent to mislead." J Med Toxicol 2008;4: 69-70.

11. Young K, **Bird S**, et al. "Productivity and Career Paths of Previous Recipients of SAEM Research Grant Awards" Acad Emerg Med 2008; 15: 560-566.

12. Ali F, Boyer E, **Bird S**. "Estimated risk of hepatotoxicity after an acute acetaminophen overdose in alcoholics" Alcohol 2008;42: 213-218.

13. Kent K, Ganetsky M, Cohen J **Bird S**. "Non-fatal ventricular dysrhythmias associated with severe salicylate toxicity" Clin Toxicol 2008; 46: 297-299.

14. Miller M, Navarro M, **Bird S**, Donovan J. "Antiemetic Use in Acetaminophen Poisoning: How Does the Route of N-acetylcysteine Administration Affect Utilization?" J Med Toxicol 2007; 3: 152-156.

15. Sivilotti MLA, **Bird SB**, Lo JCY, Dickson EW. "Multiple centrally-acting antidotes protect against severe organophosphate toxicity" Acad Emerg Med 2006; 13: 359-364.

16. **Bird SB**, Lane DR. "House officer procedure documentation using a personal digital assistant: a longitudinal study" BMC Medical Informatics and Decision Making 2006; 6.

17. Weizberg M. Su M. Mazzola JL. **Bird SB**. Brush DE. Boyer EW. "Altered mental status from olanzapine overdose treated with physostigmine" Clin Toxicol. 44(3):319-25, 2006.

18. Babu KM, McCormick M, **Bird S**. "Pediatric Dietary Supplement Use – An Update. Clin Ped Emerg Med 2005; 6: 85-92.

19. Mazzola JL, **Bird SB**, Brush DE, Aaron CK, Boyer EW. "Levofloxacin-related seizure activity in a patient with Alzheimer's disease: assessment of potential risk factors" Clin Psychopharm 2005;25:287-288.

20. Brush DE, **Bird SB**, Boyer EW. "γ-Hydroxybutyrate Use in Older Adults." Ann Intern Med 2004; 140:W70-71.

21. DE Brush, **SB Bird**, EW Boyer. "Monoamine oxidase inhibitor poisoning resulting from internet misinformation on illicit substances." J Tox Clin Tox 2004;42:191.

22. Dickson EW, **Bird SB**, Gaspari R., Boyer E, Ferris C. "Diazepam Attenuates Central Respiratory Depression Due to Organophosphate Poisoning". Acad Emerg Med 2003;10:1303-1306.

23. **Bird SB**, Gaspari R, Dickson EW. "Early Death due to Acute, Severe Organophosphate Poisoning is a Centrally Mediated Process". Acad Emerg Med 2003;10:295-298.

24. **Bird SB**, Gaspari RJ, Lee WJ, Dickson EW. "Diphenhydramine as a Protective Agent in Severe Organophosphate Poisoning" Acad Emerg Med 2002 9:1369-1372.

25. Bonkovsky H, Azar R, **Bird S**, Szabo G, Banner B "Severe Cholestatic Hepatitis Caused by Thiazolidinediones: Risks Associated with Substituting Rosiglitazone for Troglitazone" Digest Dis Sci July 2002;44:1632-1637.

26. **Bird SB**, Dickson EW. "Clinically Significant Changes in Pain Along the Visual Analog Scale" Ann Emerg Med. 2001;38:639-643.

27. **Bird SB**, Zarum RS, Renzi FP. "Emergency Medicine Resident Procedure Documentation Using a Handheld Computerized Device" Acad Emerg Med. 2001;8:1200-1203

REVIEW ARTICLES:

1. **Bird SB,** Boyer EW. "The Pharmacology and Toxicology of Ranolazine: a new metabolic modulator" IJMT 2003;6.

CORRESPONDENCES:

1. **Bird SB**, Rosenbaum CR. "Onset of symptoms after methadone overdose." Am J Emerg Med. 2008;26: 242.

TEXTBOOK SECTION EDITOR

Irwin and Rippe's Intensive Care Medicine. "Pharmacology, Overdoses and Poisonings" Section *Editor of 12 chapters*. Lippincott. 7th Ed.

Aghababian's Emergency Medicine: The Core Curriculum. Section editor of 25 chapters. Jones and Bartlett, 2nd edition.

Irwin and Rippe's Intensive Care Medicine. "Pharmacology, Overdoses and Poisonings" Section *Editor of 23 chapters*. Lippincott. 6th Ed.

BOOK CHAPTERS AND MONOGRAPHS:

Bird SB. Chromium. Goldfrank L. et al., editors. *Goldfrank's Toxicologic Emergencies,* McGraw Hill. 9th edition.

Bird SB. Organophosphates and Carbamates. Aghababian R. editor. *Emergency Medicine: The Core Curriculum.* Jones & Bartlett, 2nd edition.

Bird SB. *Manual of Intensive Care Medicine*. Rippe, and Irwin, Eds. 7th edition. **Author of 3 chapters**

Bird SB. Beta Blockers. Shannon M. et al., editors. *Clinical Management of Poisoning and Drug Overdose*, WB Saunders. 4th Ed.

Bird SB. Organophosphates and Carbamates. Aghababian R. editor. *Emergency Medicine: The Core Curriculum.* Jones & Bartlett, 1st edition.

Bird SB. Chromium. Goldfrank L. et al., editors. *Goldfrank's Toxicologic Emergencies,* McGraw Hill. 8th edition.

Bird SB. *Organophosphates and Carbamates*. UpToDate, 2004 - current.

Bird SB. *Manual of Overdoses and Poisonings*. Linden, Rippe, and Irwin, Eds. 1st edition. Lipipincott Williams & Wilkins, Philadelphia, 2005. **Author of 12 chapters.**

Bird SB. *Manual of Intensive Care Medicine*. Rippe, and Irwin, Eds. 6th edition. **Author of 3 chapters**.

ORAL PRESENTATIONS (*selected* presentations at national or international meetings):

1. Bird SB, McCall J, Sawamoto K, Khurana T. Novel Therapeutics to Protect the Neuromuscular Junction after Acute OP Poisoning. NINDS CounterACT Meeting, San Francisco, CA, 2012.

2. **Bird SB**, Carville A, Mansfield K, Ollis D. Use Of An Organophosphorus Hydrolase Prevents Lethality In An African Green Monkey Model Of Acute Organophosphorus Poisoning. SAEM 2011 Annual Meeting, Boston, MA

3. **Bird SB**, Eddleston M, Sutherland TD, Ollis D. Pharmacokinetics of an Organophosphorus Hydrolase in the African Green Monkey. SAEM 2008 Annual Meeting, New Orleans, LA.

4. **Bird SB**, Gresham H, Sutherland T, Eddleston M. Use of a Recombinant Bacterial Hydrolase for Acute Dichlorovos Poisoning. NACCT 2006 Annual Meeting, San Francisco, CA

5. **Bird SB**, Gresham H, Sutherland T, Eddleston M, Eyer P. Use of a Recombinant Bacterial Hydrolase for Acute Parathion Poisoning. SAEM 2006 Annual Meeting, San Francisco, CA.

6. **Bird SB**, Gaspari RJ, Aaron CK, Boyer EW, Dickson EW. Synergistic Effects of Glycopyrrolate, Ipratropium, and Diazepam on Mortality in a Rat Model of Lethal Organophosphate Poisoning. European Association of Poison Control Centres and Toxicologists 2003 annual meeting, Rome, Italy.

7. **Bird SB**, Mazzola JL, Boyer EW, Brush DE, Aaron CK. A Prospective Evaluation Of Abbreviated Oral N-Acetylcysteine (NAC) Therapy For Acetaminophen (Paracetamol) Poisoning. European Association of Poison Control Centres and Toxicologists 2003 annual meeting, Rome, Italy.

8. **Bird SB**, Gaspari RJ, Aaron CK, Boyer EW, Dickson EW. Nebulized Ipratropium Bromide Offers No Protection Against Severe Organophosphate Poisoning. J Tox Clin Tox 2002;40:695.

9. **Bird SB**. Critical Care Toxicology: Organophosphate Poisoning. 2002 North American Congress of Clinical Toxicology, Palm Springs, California.

10. **Bird SB**, Gaspari RJ, Lee WJ, Dickson EW. Early Death due to Acute, Severe Organophosphate Poisoning is a Centrally Mediated Process. Acad Emerg Med 2002;9:485.

11. **Bird SB**, Gaspari RJ, Lee WJ, Dickson EW. Diphenhydramine as a Protective Agent in Severe Organophosphate Poisoning. Acad Emerg Med 2002;9:357.

12. **Bird SB**. Case Presentation Competition, 2002 Society for Academic Emergency Medicine annual meeting, St. Louis, Missouri.

13. **Bird SB**, Zarum RS. Emergency Medicine Resident Procedure Documentation is Not Increased Using a Handheld Computerized Device. 2002 Society for Academic Emergency Medicine annual meeting, San Francisco, CA.

14. **Bird SB**, Sullivan J, Mangolds G, Schmidt E, Nichols C, Dickson EW. Clinically Significant Changes in Pain Along the Entire Visual Analog Scale. American College of Medical Toxicology 2001 annual meeting, San Francisco, CA.

ABSTRACTS (*selected* abstracts published and accepted for presentation at national or international meetings):

1. Weibrecht K, Dayno M, Darling C, **Bird S**. Liver aminotransferases are elevated with rhabdomyolysis in the absence of liver injury. NACCT 2009

2. Rosenbaum C, **Bird S**. Timing and Frequency of Physostigmine for Anticholinergic Toxicity. NACCT 2008

3. Acute Hepatotoxicity Associated with Amiodarone Administration Courtney J, Ganetsky M, **Bird SB**, Boyer EW. Clin Toxicol 2006; 44.

4. Isoniazid-Induced Psychosis in an Adolescent Male Gresham HW, Babu KM, Ali F, **Bird SB**, Boyer EW. Clin Toxicol 2006; 44.

5. Non – Fatal Cardiac Dysrhythimias Associated with Severe Salicylate Toxicity Kent KJ, Cohen JE, Ganetsky M, **Bird SB.** Clin Toxicol 2006; 44.

6. **Bird SB**, Schmidt K, Kulkarni P, Ferris C. M1 Receptor Activation in the rat: a phMRI Analysis. J Neuroscience.

7. **Bird SB**, Lo JCY, Dickson EW, Sivilotti MLA. Multiple centrally-acting antidotes protect against severe organophosphate toxicity.,. J Toxicol Clin Toxicol 2005; 43.

8. **Bird SB**, Dickson EW, Gaspari RJ, Boyer EW, Ferris CF. Brain functional MRI after acute organophosphate poisoning. Acad Emerg Med 2004;11:473.

9. Mazzola JL, **Bird SB**, Brush DE, Boyer EW, Aaron CK. Anticholinergic syndrome after isolated olanzapine overdose. J Tox Clin Tox 2003;41:472.

10. Brush DE, **Bird SB**, Boyer EW, Aaron CK. Geriatric Overdose of 1,4-Butanediol Masquerading as Syncope and Seizure. J Tox Clin Tox 2003;41:508.

11. **Bird SB**, Mazzola JL, Brush DE, Boyer EW, Aaron CK. A Prospective Evaluation of Abbreviated Oral N-acetylcysteine (NAC) Therapy for Acetaminophen Poisoning
Acad Emerg Med 2003;10:521.

12. **Bird SB**, Gaspari RF, Barnett KA, Dickson EW. Diazepam Attenuates Acute Central Respiratory Depression from Acute Organophosphate Poisoning. Acad Emerg Med 2003;10:520-521.

13. Lovesky D, **Bird S**, Restuccia M, Mangolds G, Dickson EW. Effect of a Paramedic Pain Management Training Program on Pre-hospital Analgesic Use. Acad Emerg Med 2003;10:450.

14. Lane DR, **Bird SB**, Zarum RS. Documentation of Emergency Medicine Resident Procedures Using a Personal Digital Assistant. Acad Emerg Med 2003;10:537-538.

15. Sivilotti MLA, **Bird SB**, Montalvo M, Aaron CK, Brison RJ, Linden CH, "Serum a-Glutathione S-transferase (aGST) Becomes Elevated Shortly After Subtoxic Acetaminophen Overdose" Acad Emerg Med 2002;9:534-535.

16. **Bird SB**, Ni Y. Comparison of a Numeric Rating Scale and the Visual Analog Scale in Extremity Pain. Ann Emerg Med 2001;38:S90.

EXTERNAL FUNDING:

Current:

"Novel Neuromuscular Protection to CounterACT Acute Organophosphate Poisoning"
Principal Investigator: **Steven B. Bird, MD**
R21 NIH/NINDS
9/1/2011-8/31/2013 $823,588

Completed:

"Use of a bacterial OP hydrolase antidote for parathion poisoning"
Principal Investigator: **Steven B. Bird, MD**
R21 NIH/NIEHS $ 446,875

Aug 2007 – Aug 2009

“Functional MRI Assessment of Acute Organophosphate Poisoning”
Principal Investigator: **Steven B. Bird, MD**
K08 NIH/NIEHS
Dec 2004 - Dec 2008 $ 580,669

“Recombinant Organophosphate Hydrolase for Acute Parathion Poisoning”
Principal Investigator: **Steven B. Bird, MD**
American College of Medical Toxicology
July 2005 – June 2006 $ 7,500

“Recombinant Organophosphate Hydrolase for Acute Dichlorvos Poisoning”
Principal Investigator: **Steven B. Bird, MD**
Emergency Medicine Foundation
July 2005 – June 2006 $ 5,000

"Ipratropium bromide as a treatment of organophosphate toxicity”
Principal Investigator: **Steven B. Bird, MD**
Emergency Medicine Foundation Resident Research Grant Award
2001 – 2002 $ 5,000

EXHIBIT 2

DESCRIPTION	BATES RANGE
Agent/Stimulant Name	DVA003 010053-64
Andrews, P. *et al.*, "Evaluation of Atropinization by Various Routes in Humans," Contract Report, MLCR No. 59, July 1955	JK15 0021612-27
Army Inspector General Report on Use of Volunteers in Chemical Agent Research	VET004_001665-938
Army Regulation 70-25, Use of Volunteers as Subjects of Research	Deposition Exhibit 94
Army Regulation70-25, Use of Volunteers as Subjects of Research	Deposition Exhibit 311
Bartosova, L. *et al.*, "The Acute Toxicity of Acetylcholinesterase Reactivators in Mice in Relation to Their Structure," *Neurotox. Res.* 2006, 9(4), 291-296	
Bouchard, M.F. *et al.*, "Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children," *Environ. Health Perspect.* 2011, 119, 1189-95	
Breyer-Pfaff, U. *et al.*, "Neuromuscular Function and Plasma Drug Levels in Pyridostigmine Treatment of Myasthenia Gravis," *J. Neurol. Neurosurg. Psychiatry* 1990, 53, 502-506	
Brown, M., "Military Chemical Warfare Agent Human Subjects Testing: Part 1—History of Six Decades of Military Experiments with Chemical Warfare Agents," *Military Med.* 174(10), 1041-1048	
Brown, M., "Military Chemical Warfare Agent Human Subjects Testing: Part 2—Long-Term Health Effects Among Participants of U.S. Military Chemical Warfare Agent Testing," *Military Med.* 2009, 174(10), 1049-1054	
BZ Dose and Dose Response Data	JK04 0005418-41
Cannard, K., "The acute treatment of nerve agent exposure," *J. Neurol. Sci.* 2006, 249, 86-94	
Chemical Warfare Agent Experiments Among U.S. Service Members, Department of Veterans Affairs, Washington, D.C., Updated August 2006	VET001_015675-707; Deposition Exhibit 554
Chemical Warfare Agents, Toxicology and Treatment (Marrs, Maynard & Sidell, eds., 2d ed. Wiley & Sons, Ltd. 2007), Ch. 29, pp. 663-708	PLTF 009306-50
DAIG-IN-21-75, Use of Volunteers in Chemical Agent Research, Chapter VI, Informed Voluntary Consent	
Defendants' Decoded List of Testing Agents	DVA006 027342-50
Defendants Department of Defense and Department of the Army's Objections and Responses to Plaintiffs' Amended Set of Requests for Admission, August 15, 2011	

Department of Veterans Affairs Training Letter, Department of Defense (DoD) Identifies Additional Service Members Who Participated in the Testing of Chemical and Biological Warfare Agents During Service, September 12, 2006, Attachments A-C, DVA Outreach Letter, Fact Sheet, and Frequently Asked Questions	VET001-015121-34
Dille J.R. *et al.*, "Central Nervous System Effects of Chronic Exposure to Organophosphate Insecticides," *Aerosp. Med.* 1964, 35, 474-8	
Duffy, F.H. *et al.*, "Long-term effects of an organophosphate upon the human electroencephalogram," *Toxicol. Appl. Pharmacol.* 1979, 47, 161-76	
DVA Benefits Administration Training Letter 06-04, Re: DoD Identifies Additional Service Members Who Participated in the Testing of Chemical and Biological Warfare Agents During Service	VET001_015121-34
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