Assessment of Potential Long-Term Health Effects on Army Human Test Subjects of Relevant Biological and Chemical Agents, Drugs, Medications and Substances

SUPPORT SERVICES

Literature Review and Analysis

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ALL NATIVE
GROUP

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Executive Summary

Background

Between 1954 and 1975, more than 12,000 men entering or in military service in the United States (US) volunteered as medical research subjects for the country's biological and chemical warfare defense programs[1]. With their consent, some of these servicemen served as human volunteers in exposure experiments to a wide variety of biological and chemical substances, medications, vaccines, or simulants. The purpose of these tests was to use volunteers to evaluate the effect of biological and chemical substances on humans in an effort to determine US vulnerability to attack.[1,2,3,4] The three main programs under which this testing took place were Project Whitecoat, Project 112, and Project SHAD (Shipboard Hazard and Defense.)

Several reviews of the health status of volunteers in these exposure experiments have been done the years following the original studies and have found no conclusive evidence that receipt of investigational agents or substances was related to adverse health outcome[1,2,3,4] None of the follow-up studies or reviews found differences in all-cause mortality between participants and controls, and none of the studies found consistent, clinically-significant groups of symptoms in those exposed. Despite these failures to determine that the tests had a long-term negative effect on the health of the men who participated in the exposures, many test participants continue to self-report their health as consistently lower than the health of non-participant controls.

The purpose of this report is to provide documentation of potential long-term health effects of exposure to the agents, compounds and drugs tested. Literature searches and analyses of scientific and medical studies published between June 30, 2006 and December 1, 2015 have been reviewed for information concerning the potential long-term health effects of the volunteer human exposures.

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[1] The total number of volunteers is based on a combination of figures given in the 1985 National Academies of Science review (vol. 3) of the long-term health effects of volunteer exposure (ref 4), and the 2007 Institute of Medicine's review of the SHAD project, (ref 387). These reports state that, "at least 12,520 military personnel volunteered," (more than 5,800 for the SHAD project, and a total of 6,720 for Operation Whitecoat and Project 112) to be subjects. The number of military who were exposed to chemicals is also unclear. For example, the executive summary of the NAS report (ref 4) states that, "4,826 were exposed to some experimental chemicals." The introduction (paragraph 3, sentence 1) of the same document reads, "15 anticholinesterase chemicals and 24 anticholinergic chemicals had been administered to some 3,200 subjects." There is a supposed breakdown of this 3200 in the last part of the paragraph that actually adds up to 3,325 subjects who received exposures. So it is difficult to count the actual exposures.

Evidence found in the literature for potential long-term health effects or sequelae does not necessarily mean that these symptoms have occurred or will occur in subjects from the military testing programs. Evidence for potential sequelae only means that these conditions *could* occur in the soldiers who participated in the tests.

Results

Of the more than 100 agents and compounds researched for this study, 18 had evidence for potential long-term sequelae associated with exposure (See Table 1.) There were 16 different types of sequelae that ranged from neurological disorders to carcinomas. The most frequently seen sequelae were neurological, which occurred in 7 of the 18 compounds. The next most common types of sequelae were cognitive, cardiac, and cutaneous which were each noted in 5 compounds. A higher risk of sarcomas or carcinomas were noted in those exposed to 4 substances. Some types of sequelae were noted only in association with one compound, as in the case of movement disorders (dystonias and dyskinesias) and butyrophenone derivatives.

Sequelae by Compound or Substance

The anticholinesterases had the largest number of sequelae associated with them, with five out of 10 compounds associated with the long-term negative effects of exposure. By comparison, only three of 15 biological agents or vaccines had information about related sequelae in the recent scientific or medical literature.

Sulfur mustard had the largest number of sequelae associated with it, and these ranged from respiratory problems to psychosocial and cognitive issues. Some compounds, on the other hand, were outdated or experimental and obscure and little or no information could be found about their long-term adverse effects. To some degree also, estimations of, "the most" or "the least" sequelae have a certain amount of study bias associated with them. For example, most of the data on potential sequelae from sulfur mustard comes from long-term studies of soldiers exposed during the Iran-Iraq War. The doses these men received in theatre were massive when compared to the exposures of the volunteer test subjects. A more detailed discussion of sequelae can be found in the body of the paper.

Although evidence for long-term sequelae associated with exposure to some agents and substances was found in the recent scientific literature, it is important to note that:

- Volunteer exposures were low relative to many of the sequelae-inducing doses in the recent literature;
- Volunteer exposures were single dose or short term, whereas many of the sequelae reported in the recent literature arose after long-term or chronic exposures;

- Tests were terminated immediately if the volunteers experienced moderate-to-severe discomfort; and
- The health impact of volunteers was assessed at several different time periods in the years following their exposures, and no significant sequelae were recorded in any of the follow-up health screenings.

Furthermore, some of the information presented in this report about associated sequelae comes from animal studies. This information is informative, but should not be taken as indicative of sequelae associated with human exposure to these compounds. Rather the animal experiments should be regarded as, "proof of concept," of sequelae that might arise in humans after exposure, or as supportive of human epidemiological and medical data, if available.

Table 1. Potential Long-Term Sequelae from Exposure to Agents or Compounds in this Study

Agent or Compound	Neuro-logical	Cognitive or Learning	Depression	Fatigue	Psycho-social	Anxiety	Cardiac or Vascular	Muscle Weakness	Movement	Respira-tory	Neuro-endocrine	Bowel	Cutane-ous or Allergic	Ocular	Blood or Marrow	Cancer
C. burnetii	X			X			X									
EEE/WEE/VEE	X															
C. botulinum	X			X				X								
Tabun	X	X						X								
Sarin	X	X				X	X			X	X					
Soman						X										
DFP	X	X														
Malathion		X	X													X
Lysergamides					X		X									
CS													X			
Butyrophenone derivatives							X		X							
Sulfur Mustard	X	X			X	X				X			X	X		X
Phosgene										X						
Dioxins	X												X			X
Arsenic							X						X			X
Chloram-phenicol															X	
Tetracycline												X				
PABA													X			

Introduction

Between 1954 and 1975, more than 12,000 men entering or in military service in the United States (U.S.) volunteered as medical research subjects for the country's biological and chemical warfare defense programs[2]. With their consent, some of these servicemen served as human volunteers in exposure experiments to a wide variety of biological and chemical substances, medications, vaccines, or simulants. The purpose of these tests was to use volunteers to evaluate the effect of biological and chemical substances on humans in an effort to determine U.S. vulnerability to attack.[1,2,3,4] The three main programs under which this testing took place were Project Whitecoat, Project 112, and Project SHAD (Shipboard Hazard and Defense.)

This report focuses on the different agents used in these exposure studies. These agents include wide variety of biological and chemical warfare agents, vaccines, irritants, incapacitants, and many miscellaneous compounds and drugs. Many of these chemical agents cause acute symptoms including hallucinations, blurred vision, eye irritation, and acute respiratory symptoms. In the years following these exposure studies, concerns about the long term health effects of these exposures have been brought up by military personnel leading to multiple studies and reviews on the long term health impacts.

Several reviews of the health status of volunteers in these exposure experiments have been done the years following the original studies and have found no conclusive evidence that receipt of investigational agents was related to adverse health outcomes.[1,2,3,4] None of the follow-up studies or reviews found differences in all-cause mortality between participants and controls, and none of the studies found consistent, clinically-significant groups of symptoms in those exposed. Despite these failures to determine that the tests had a long-term negative effect on the health of the men who participated in the exposures, many test participants continue to self-report their health as consistently lower than the health of non-participant controls.[3]

The purpose of this report is to provide documentation of potential negative long-term health effects (sequelae) of exposure to the agents, compounds, and drugs tested. Literature searches and analyses of scientific and medical studies published between June 30, 2006 and December

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[2] See footnote 1.

[3] In the follow-on health status studies, participants were divided into exposure groups, and were matched with non-participant controls. In general, the reviews found no statistical difference in health between participants and nonparticipant controls. A more detailed discussion of participants vs. controls is available in the Institute of Medicine review of Project SHAD volunteer health (ref 387)

1, 2015 have been reviewed for information concerning the potential long-term health effects of the volunteer human exposures. Some papers consulted or cited on health outcomes in exposure-test participants were published prior to 2006. This report will be used to inform an ongoing legal case brought by former test subjects against the Central Intelligence Agency, Department of Defense and Department of the Army.

What are Sequelae?

Sequelae are secondary symptoms that can persist for weeks or sometimes for months or years after an original exposure or infection.

In cases of sequelae following infections, generally the sequelae are not associated with a persistent or reactivated primary infection, but rather result from a separate disease or condition *triggered* by the original infection. For example, some infections (i.e. infection with *Clostridium botulinum)* can cause severe fatigue in some individuals that lasts for months or years after the infection has been eradicated.

Sequelae differ from complications of exposure or infection by the timing of onset of symptoms: complications occur during exposure or infection and may pose obstacles to treatment, whereas sequelae arise after initial symptoms and become separate conditions or diseases. With proper treatment, complications will usually resolve as infection resolves or as the amount of agent or substance in the body clears. Sequelae can persist despite proper treatment and substance clearance.

Sequelae usually arise in the weeks or months that follow an exposure or infection. Rarely, if ever, have they been recorded happening for the first time years after the initial exposure and primary symptoms. Also, sequelae *can be* associated with exposures and infections but do not *always* occur. Only a fraction of the people exposed to a substance may develop sequelae as a consequence.

The relevance to military test subjects in Whitecoat, Project 112, and SHAD are that for their symptoms to even be considered as potential sequelae of exposure, the conditions experienced by the volunteers in the military human trials must have arisen in the weeks or months following exposure, not five to ten years (or more) after exposure. Given this timing, potential sequelae should have been detected in the follow-up health screenings given to test participants.

Sources of Information

The types of information evaluated as a part of this review varied widely from medical case reports and long-term health monitoring of exposed soldiers, to animal studies and clinical trials,

to meta-analyses that combine the results of several studies for trend analysis and statistical significance. These sources also vary widely in the value of the information that they provide.

For example, some of the information presented in this report about associated sequelae comes from animal studies. This information is informative, but should not be taken as indicative of sequelae associated with human exposure to these compounds. Rather the animal experiments should be regarded as, "proof of concept," of sequelae that *might* arise in humans after exposure, or as supportive of human epidemiological and medical data, if available.

Likewise, a great deal of the recent public health and medical literature consulted for this study involves sequelae that may arise from long-term exposures or chronic use of a medication or substance. By contrast, the volunteer tests consisted of a single exposure or on occasion, a short series of exposures. Additionally, exposure doses in the literature consulted can be extremely high relative to the doses administered to volunteer test subjects.

The information offered by medical case reports is also potentially problematic. They differ from scientific studies in several important ways. Medical case studies are:

- Usually only based on one or two cases per publication;
- Often based on the accepted or status quo interpretation of symptoms or disease states; and
- Sometimes numerous in the literature relative to other types of reports or studies.

Taken together, these issues with medical case reports can affect the understanding of a disease or condition. An example of this can be found in literature on LSD and other hallucinogens. The plethora of medical case reports discussing negative sequelae (flashbacks) to hallucinogen exposure influenced medical opinion for decades about the effects of these drugs. It wasn't until recent population-level studies of effects showed that no harmful sequelae were associated with hallucinogen use that the conclusions of these case reports were questioned.

The relevance of this to the health of military test subjects is that older literature (prior to June 30, 2006) and medical case studies may report sequelae associated with the agents in this report, whereas more modern scientific or population-based studies show no association. Thus some of the results communicated in this report may contradict that of earlier reports.

Screening Before and After Testing

The records of the tests published by the National Academies of Science in the 1980s showed that the volunteers were carefully screened prior to the tests; exposures were low relative to many of the sequelae-inducing doses in the recent literature; and the tests were terminated immediately if the volunteers experienced moderate-to-severe discomfort. Additionally, the health of volunteers was assessed at several different time periods in the years following their exposures, and no significant sequelae were recorded in any of the follow-up health screenings.

1.0 Agents and Substances with Evidence for Long-Term Sequelae

1.1 Classical Biological Agents and Vaccines

Table 2. Biological Agents with Potential for Long-Term Sequelae
Coxiella burnetii (Q-fever)
Eastern, Western, and Venezuelan Equine Encephalitis Viruses
Clostridium botulinum (Botulism)

Coxiella burnetii (Q-fever)

After primary infection with *C. burnetii*, approximately one-to-five percent of patients' progress to chronic infection in the years following initial infection.[5] A common symptom of chronic Q-fever is endocarditis, which can occur months or years after infection, and can be fatal if untreated. It can also be treated as a long-term sequelae of Q-fever because it can emerge long after the original infection, and persist after the recurring infection has been eradicated. Other long-term sequelae have been reported such as chronic fatigue,[5,6] vascular infections,[7,8,9] and neurological impairments.[10,11,12]

Chronic Fatigue

Persistent fatigue following acute infection with *Coxiella burnetii* is the most common long-term sequelae reported following acute Q-fever.[5,6] The symptoms associated with this are disabling fatigue, musculoskeletal pain, neurocognitive difficulties, and mood disturbance. These symptoms can last for months or years after eradication of the primary infection. Although these symptoms are associated with morbidity more than mortality, they can be severe. One study found over eight times more (per 1000 cases) disability-adjusted life years associated with post Q-fever fatigue than with pandemic influenza.[13]

The cause of the fatigue symptoms after primary infection is unclear. Some authors have hypothesized that a dysregulation of cytokines (i.e., increased IL-6 release),[7] or impaired immune function in general might be associated with chronic fatigue,[14] while others think that the persistence of *C. burnetii* organisms (antigenic non-viable cell residues) in the host's bone-marrow[15] or changes in immunogenetics[16] might account for post Q-fever fatigue.

A study published in September 2006 by Hickie et al., was instrumental in providing evidence for the long observed phenomenon of severe fatigue following acute Q-fever.[17] The study, a

prospective cohort study of 253 patients in rural southwestern Australia, found that 12 percent of patients developed symptoms of chronic fatigue after a laboratory-confirmed infection with *Coxiella burnetii*.

More recent studies have found a higher percentage of severe-fatigue symptoms following acute Q-Fever infection. For example, in a recent review of the Q-fever outbreak in The Netherlands, over 50 percent of patients were suffering from severe fatigue symptoms (compared to 26% of the control group), one year after their initial infection.[18,19] This study involved 54 patients from the same geographical outbreak area with 23 age and sex-matched controls from the same neighborhood.[19] It is difficult, however, to compare the results between studies, because they do not all differentiate between fatigue symptoms, idiopathic chronic fatigue, and chronic fatigue syndrome.

Some studies have questioned whether post-infection fatigue symptoms could be correlated with other psychological variables such as pre-infection depression or neuroses, but the results are equivocal. A 2012 German study by Strauss et al., found that patients who were exposed to a *C. burnetii* infection indicated increased post-infection fatigue symptoms (54.8 percent vs. 20 percent) and chronic fatigue than controls (32 percent vs. 4.7 percent).[6] This study followed 84 patients approximately 2 years after infection and a matched control group of 85 patients with the same general practitioners. It was also noted that patients with higher fatigue scores also scored significantly higher on psychological tests examining somatoform disorders (SOMS) and hypochondria (Whitley-Index), indicating that psychosocial factors might play a role in the self-perception of post-infective fatigue.[6]

The previously mentioned Australian study by Hickie et al., was controlled for demographic and psychological issues, but found that neither had a significant effect on the incidence or severity of post-infective fatigue.[17] However, the study did find that severity of acute symptoms during infection with *C. burnetii* was predictive of chronic fatigue symptoms, with the most severe cases of Q-fever resulting in long-term fatigue. [17]

Work on the association of Q-fever with fatigue related long-term sequelae is ongoing. For example, a team of researchers who showed that whole blood gene-expression in Q-fever-related fatigue is identical in individuals with long-term idiopathic fatigue,[16] is continuing its work, and the randomized, placebo-controlled study is examining the effect of antimicrobial treatment on Q-fever related fatigue symptoms.[5]

Vascular Complications: Endocarditis and Other Vascular Infections

After primary infection with *C. burnetii*, approximately one-to-five percent of patients' progress to chronic infection in the years following initial infection.[5] Endocarditis, mycotic aneurysm, and vascular infection are the most common manifestations.[20] These sequelae will be discussed because they can persist after active infection appears to be eradicated and have an extremely poor prognosis if untreated, with mortality approaching 100 percent and the need for surgery of up to 60 percent.[21] Patients with pre-existent valvular disease or vascular defects, immunocompromised patients, or pregnant women, are most frequently affected.[22]

Additionally, secondary aneurysm or vascular infection can occur after treatment for *C. burnetii* related endocarditis has started.[9] The estimated risk of transformation from acute infection to Q-fever endocarditis in patients with preexisting valvulopathy is approximately 40 percent.[8] In the literature, association of endocarditis and vascular infection with Q-fever is difficult to find. Good evidence for the association is usually only found in individual case studies as opposed to epidemiological studies on infected populations.

More recently however, long-term study of patients from a large outbreak (>4000 cases) in the Netherlands in 2007 has resulted in more cases of vascular complication following Q-fever. For example, a 2014 study from the Netherlands has shown that 30.8 percent of patients with aortic or iliac disease living in an epidemic area are seropositive for *C. burnetii*.[9] This is much higher than the 7.8 percent seropositive rate found in Dutch patients with a history of cardiac valve surgery living in the same epidemic area.[23] This suggests there is a higher than previously understood association between Q-fever infection and vascular complications. This increase in the size of the data pool may lead to a better understanding of the association as well as additional long term sequelae in future years.

Neurological Impairments

Acute neurologic manifestations following acute *C. burnetii* infection include headache, encephalitis, encephalomyelitis, meningitis, Guillain–Barré syndrome, optic neuritis, brachial neuritis, mononeuritis multiplex, peripheral neuropathy, transverse myelitis, polyradiculopathy, and extrapyramidal disorders.[10,11,12] Central nervous system neuropathies can be seen in as many as 40 percent of post-infective Q-fever patients, but peripheral disturbances are reported in less than one percent of patients. The peripheral neuropathies that have been reported include brachial-plexus neuropathy usually manifesting itself as pain in the shoulder and hip, numbness in the radial aspect of the forearm and deltoid area, or difficulty in raising the arm.[10] Other peripheral neuropathies include transient or recurring optic neuritis.[11,12] All of the peripheral neuropathies were successfully treated with long-term antimicrobial therapy.[10,11]

Cognitive Problems

A 2013 study by Cvejic and colleagues looked at neurocognitive sequelae in 121 Australian patients infected with Epstein Barr virus, *C. burnetii* (21 patients), or Ross River virus.[24] Study subjects exhibited slower matching-to-sample responses, poorer working memory capacity, mental planning, and dual attention task performance.[24] Objective impairments correlated significantly with self-reported symptoms as well as levels of the inflammation marker, C-reactive protein.[24] This study also attempted to understand the underlying causes of the neurological sequelae. Linear regression analysis identified an association between neurocognitive disturbance and functional polymorphisms in inflammatory cytokine genes.[24] Specifically, the high cytokine producing G allele of the IL-6-174G/C SNP was associated with poorer neurocognitive performance. These findings suggest that genetic polymorphisms may predispose some individuals to more intense inflammatory responses that may result in neurocognitive disturbances following acute infections.[24]

Eastern, Western, and Venezuelan Equine Encephalitis Viruses

It is estimated that up to thirty percent of survivors of encephalitis resulting from eastern equine encephalitis virus (EEEV) or western encephalitis virus (WEEV) experience severe neurological sequelae.[25] In Venezuelan equine encephalitis virus (VEEV), on the other hand, neurological disease, including disorientation, ataxia, mental depression, and convulsions can be detected in up to 14 percent of infected individuals.[25] Neurological sequelae from VEEV infection in humans are also common.[25]

Neurological Impairments

Half of those who survive EEE suffer permanent neurologic sequelae and require long-term care, which is estimated to cost as much as three million dollars per patient over the rest of their lifetime.[26] A study done in Darién, Panama, found that of seven cases of EEEV-associated encephalitis (or dual infection with VEEV) admitted to hospital, three were discharged with severe neurological sequelae, which included recurrent seizures, psychomotor impairment, or a vegetative state.[27]

A review of fifteen EEE cases in Massachusetts and New Hampshire from 1970 – 2010 also revealed that 33 percent of EEE patients developed severe neurological impairments and an additional 13 percent had mild neurological deficits at discharge.[28] Of four patients with severe deficits at hospital discharge, three showed improvement at follow-up (follow-up was unavailable for one patient with severe neurological impairments). One patient progressed from being comatose to being able to communicate nonverbally by 30 months after hospital discharge. A second patient recovered speech, comprehension, and the ability to self-feed by 18 months after hospital discharge, and a third patient progressed from being nonvocal and having limited

spontaneous movements when released from the hospital, to speaking in full sentences by 21 months after discharge.[28]

Interestingly, poor case outcome for EEE was correlated with the length of the prodromal illness phase, with those patients with the shortest prodrome having the worst long-term follow-up symptoms. This could be because of variation in neuroinvasiveness, fitness, or virulence of different strains of virus,[29] because of host factor variability,[30] or exposure to substances that damage the blood-brain barrier and enhance neuroinvasiveness.[31]

In addition to long-term health effects resulting from encephalitis or encephalomyelitis, there are case reports that include sepsis and myocarditis in addition to neurological symptoms. These severe complications could also potentially have their own sequelae.[32]

Clostridium botulinum (Botulism)

Those who survive an episode of botulism may have fatigue and shortness of breath for years. Self-assessments of psychosocial well-being have also shown patients recovering from botulism rate themselves less well off than age and sex-matched controls. Most sequelae reported from botulism intoxication are neurological in origin.[33]

Fatigue and Neurological Impairments

The most complete survey of long-term health following botulism to date has been done in patients recovering from disease in the Republic of Georgia.[33] Gottlieb and colleagues interviewed 211 patients recovering from botulism, and found most sequelae from intoxication to be neurological in origin. Sixty percent of recovering patients rated their health, "fair," or, "poor," as opposed to only 20 percent of control subjects. Patients were also significantly more likely than control subjects to report current symptoms of fatigue, weakness, dizziness, dry mouth, and difficulty lifting things ($P < 0.05$

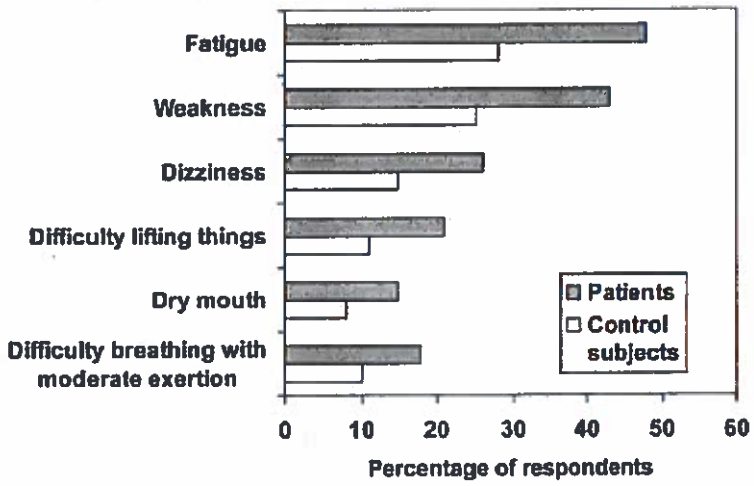


Figure 11. The figure shows the percentage of respondents who reported that for "a good bit," "most," or "all" of the time in the past 4 weeks, they felt the emotional factors shown in the figure. (Source: Gottlieb, et al., 2014.)

for each symptom; see Figure 1.)[33]

Twenty-five percent of patients enrolled had required mechanical ventilation during the acute phase of their illness. These patients, presumably with more severe disease, had significantly worse health outcomes than patients who did not need assistance breathing.

A small outbreak of botulism resulting from the ingestion of home-brewed alcohol in a Utah prison in 2011 resulted in some sequelae lasting 11 months after the outbreak. Clinical complaints included weakness and loss of muscle mass, dysphagia and reflux. Difficulty sleeping, increased anxiety, and depression also were reported, prison medical staff did not associate these with the botulism incident.[34]

An animal study by Frick and colleagues supports the findings from the Republic of Georgia by showing how even a single injection of botulinum toxin can have crippling effects that last for months after the injection.[35] In this study, rats were injected with varying doses (0.625, 2.5, and 10 U) of botulinum toxin into the tibialis muscle. Control animals received an equivalent volume of saline. At 128 days after injection, neuromuscular function and expression of nicotinic acetylcholine receptors (nAChRs) were evaluated. These authors found that nerve-evoked tensions, including tetanic tension and muscle mass, were decreased on the toxin-injected side in a dose-dependent manner relative to saline-injected controls as well as the contralateral side.[34]

Full or partial paralysis continues after exposure because of the persistence of the toxin at the neuromuscular junction. Research indicates that the persistence of BoNT intoxication can be influenced both by the ability of the toxin protease or its cleaved SNARE (soluble Nethylmaleimide-sensitive factor attachment protein receptor) protein substrate to resist turnover.[36] Since protease turnover seems to be mediated in part by the ubiquitin-proteasome system (UPS) research continues to manipulate the UPS to improve development of botulism antidotes.[35]

1.2 Anticholinesterases

Table 3. Anticholinesterases with Potential for Long-Term Sequelae
Tabun (GA)
Sarin (GB)
Soman (GD)
DFP (Diisopropyl fluorophosphate)
Malathion

Tabun (GA, EA 1205)

Survivors of Tabun exposure can exhibit a number of long-term sequelae including neurological and cognitive impairments and severe muscle weakness that inhibits mobility or other activities.

Neurological and Cognitive Impairments

Tabun exposure can produce centrally mediated seizure activity, which rapidly progresses to status epilepticus, contributing to profound brain damage. The exposure of experimental animals to tabun in convulsion-inducing doses may result in irreversible lesions in the central nervous system (CNS) that can be manifested as behavioral effects in survivors who have convulsed. Additionally, there are numerous studies in both humans and animals showing that survivors of high-level nerve agent exposure can experience subtle but significant long-term neurological and neuropsychological outcomes that are detectable months or even years following the recovery from acute poisoning.

For example, a long-term clinical follow-up study of severely exposed survivors of Tabun and sulfur mustard attacks during the Iran-Iraq war found neurological complications of exposure 20-27 years after exposure.[37] Specifically, this study found that sensory nerve impairments, including paraesthesia (88.3%), hyperaesthesia (72.1%) and hypoesthesia (11.6%), were the most common observed clinical complications in the survivors. The prevalence of these complications were prominently higher (72.1% hyperaesthesia and 11.6% hypoesthesia) than the adult neuropathy prevalence of 3.3–8%.

Animal studies also indicate long-term cognitive impairments in rats given a low-level tabun exposure.[38] In a study, Kassa and colleagues found impaired visuospatial working-learning performance of rats in a water maze that was believed to reflect the ability of the subject to retain trial-dependent information in memory.

Muscle Weakness

Another one of the long-term health effects of exposure to tabun is muscle weakness and lack of muscle control which can manifest as full or partial paralysis, or simply weak muscles.

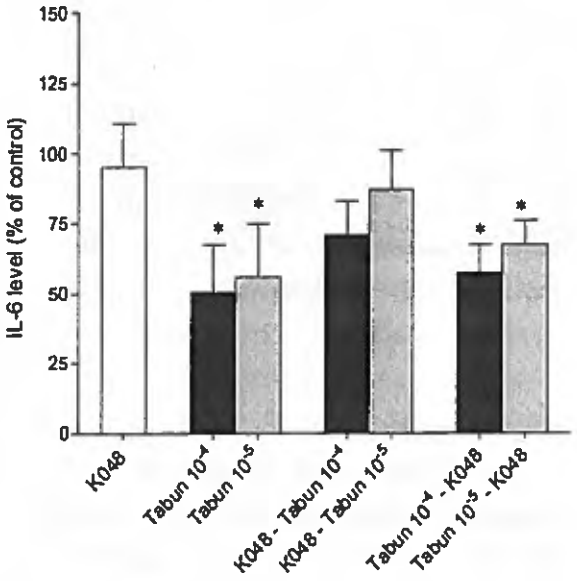


Figure 2. Decrease in Myoblast IL-6 Levels with Tabun Exposure. (Pyridinium oxime K048 is used as the comparison or companion compound) Credit: Katalinic, 2013

The mechanisms underlying these symptoms are not completely understood, but *in-vitro* studies on human myoblasts have shown that ten-minutes of either 10^{-5} M or 10^{-4} M tabun exposure produces a near 100% drop in acetylcholinesterase (AChE) activity in the cells as well as a 53% decrease in secretion of IL-6 (See Figure 2), coupled with a concomitant 34% increase in some heat-shock proteins.[39] Since AChE in believed to be involved with apoptosis in myoblasts prior to regeneration[40] and IL-6 is a potent stimulator of regeneration,[41] it is possible that these changes in myoblast secretion may result in a marked decrease in myoblast regenerative function after exposure.

Sarin (GB, EA-1208)

Neurological and Cognitive Impairments

Longitudinal clinical evaluation of the victims of the sarin attacks on the Tokyo subway suggest that there have been long-term neurological and cognitive sequelae from exposure.[42] In a study of 38 survivors of the Tokyo attack who were treated for acute sarin intoxication, Yamasue and colleagues found that most of the subjects suffered from somatic complaints, ocular symptoms, and memory loss, even though the neuropsychological and occupational impairments were relatively mild. Importantly, these researchers also found significant decreases in regional gray matter volume in the right insular and right temporal cortices, in the left hippocampus. They also found decreases in regional white matter volume in the left temporal stem of victims of sarin exposure when compared with matched control subjects. Furthermore, reduced regional white matter volume of the left temporal stem was significantly related to the long-term somatic complaints of the victims.[41]

A potential confounding factor related to the Yamasue study is the inability to completely differentiate the effects of sarin intoxication from psychological stress and trauma such as post-traumatic stress disorder (PTSD). Previous studies have indicated changes in brain structures in victims of PTSD that were not exposed to chemical agents.[43,44] However, Yamasue and colleagues did perform a separate analysis of covariance looking for the effects of psychological stress on gray matter density. They did not find a significant correlation between regional brain volume reduction and psychological symptoms.

In another case well documented by Loh, a Gulf War Veteran exposed to sarin as part of his IED disposal duties developed cognitive disturbances months after his single sarin exposure.[45] He complained of short-term memory loss, mostly involving names and tasks that he intended to complete. He also noted episodic dyscoordination and imbalance. He was assessed after he had fallen several times for no reason and began to weave down straight hallways on occasion, without any noticeable cause.

Studies in rodents have also found that inhalation of sarin vapors induced impaired memory processes at 1-month post exposure with no recovery of function during the 6 months follow-up period.[46] Studies examining the mechanism of exposure-related long-term deficits in rats have shown that organophosphorus poisons interfere with microtubule polymerization.[47] Since microtubules are required for transport of nutrients from the nerve cell body to the nerve synapse, it has been suggested that disruption of microtubule function could explain the learning and memory deficits associated with OP exposure.[49] Additionally, increased peripheral benzodiazepine receptors in microglia have been found for up to six-months following a single exposure to sarin, suggesting another mechanism for impaired performance in learning and memory tasks.[49]

Cardiac Abnormalities

A study conducted at Wright State University using sarin-exposed mice suggested that even a low dose of sarin can have severe effects on the autonomic nervous system, as related to heart rate variability, baroreflex function, and a central marker for adrenergic activity.[48] Animal studies using echocardiography, electrocardiography, and histology to determine sarin's effect on the murine cardiovascular system also found that the sarin plays a role in cardiac remodeling and reducing cardiac performance.[49] Specifically, this study found that sarin exposure caused marked increases in heart weight to body weight ratios and decreases in the left ventricular lumen size. In addition, cardiomyocytes were significantly larger in the sarin-exposed mice and atrial/brain natriuretic peptide levels were increased. Lastly, results of the electrocardiograms showed significant ST/T-wave changes in the sarin group, while the echocardiograms showed significantly decreased performance of the left ventricle.[48]

Neuroendocrine Abnormalities

A study in rats done at the Lovelace Respiratory Research Institute found that inhalation of sub-clinical doses of sarin, which did not cause overt signs of cholinergic toxicity or detectable changes in the brain AChE activity, still induced long-term decreases in the production of the adrenocorticotropic hormone (ACTH) ($p < 0.01$) from the pituitary and cortisol/corticosterone (CORT) ($p < 0.05$) from the adrenal glands.[50] Low CORT and ACTH contribute to a wide range of symptoms in other diseases, including muscle weakness, chronic fatigue, dizziness, and headaches, but it is unclear what the impact of these decreases may be following sub-clinical exposure to sarin.

Anxiety

Victims of the Tokyo and Matsumoto sarin attacks have reported symptoms associated with anxiety disorders over a decade after the attacks.[51] These anxiety disorders, including posttraumatic stress disorder (PTSD) – the most prevalent neuropsychiatric deficit present in the sarin attack victims in Japan[52] – are associated with amygdalar hyperactivity[53] and volumetric loss.[54]

Respiratory Impairments

The Kurdish population in the northern Iraqi mountains was subject to chemical weapons attacks with a range of agents, including sarin, tabun, soman and blistering agents such as sulfur mustard. These attacks were launched by Iraqi government, most notably in Halabja and Sheikh Wassan. Survivors of these attacks have reported multiple respiratory symptoms, sometimes for many years following the attacks.[55] These symptoms include shortness of breath, cough, and severe wheezing.[56] Although the most severe long-term symptoms are associated with exposure to blistering agents in this population, survivors without blistering at the time of the attacks also have long-term impairments to the respiratory systems.[57]

Soman (GD, EA 1210)

Soman exposure in both human and animals produces long-term anxiety disorders in some individuals. This association is seen with both high and low dose exposures. Additionally, transient neurological and cognitive disturbances are also found.

Anxiety

Anxiety disorders are commonly reported by survivors of accidental or deliberate exposure to anticholinergic organophosphate nerve agents.[58] Human survivors of acute sarin intoxication received during the Aum Shinrikyo attack on the Tokyo Subway demonstrated anxiety disorders

for many years following exposure.[57] Animal studies support these findings with some reporting that a single exposure to sub-lethal doses [0.6 LD_{50} (16.8 mg/kg) or 0.8 LD_{50} (22.4 mg/kg)] of soman can trigger long-lasting anxiogenesis and decreased locomotor activity in guinea pigs.[57]

There have also been recent advances in understanding the mechanism of this anxiety. A recent study of soman-exposed (149 mg/kg, approximate dose of 1.35 LD_{50}) mice found significant damage to the function of the gamma-aminobutyric neurotransmitter system (GABAergic system) in the basolateral amygdala (BLA), resulting in significantly increased tonic excitatory activity.[59] Thus the anxiety reported by some survivors of the Tokyo attacks may be attributable to BLA hyperexcitability instead of nonspecific "stress."

DFP (Diisopropyl fluorophosphate)

Epidemiological studies of adults and children exposed to DFP have found long-term cognitive deficits that persist for years after organophosphate intoxication. Animal studies, on the other hand, seem to indicate that most cognitive deficits resolve if behavioral testing continues beyond DFP exposure and into a washout period. The differences between the human and animal findings may be dose dependent.

Neurological and Cognitive Impairments

The U.S. Environmental Protection Agency estimates that millions pounds of organophosphate (OP) pesticides are used each year in the United States.[60] Despite the widespread use of these chemicals, some epidemiological studies have reported prolonged neurological changes following OP intoxication.[59]

Human Studies

These studies indicate that individuals intoxicated by OPs can exhibit long-term deficits in cognitive and motor processes including abstraction, dexterity, memory, problem solving, visual attention and visuomotor speed.[59] One study comparing the long-term sequelae of organophosphate intoxication with those of other pesticides or toxic substances such as kerosene found that children who had been exposed to organophosphate pesticides had a deficit in inhibitory motor control, almost ten years after exposure when compared to controls ($p < 0.01$).[61]

Animal Studies

Animal studies have found that repeated sub-clinical exposures to DFP can also lead to prolonged deficits in cognition.[62,63] One study examined behavioral responses in rats injected with DFP of 0.5 mg/kg every other day for 30 days. Behavioral testing occurred daily during the DFP-

exposure period and throughout a 45 day (OP-free) washout period. When compared to controls, DFP-treated rats exhibited deficits in accuracy ($p < 0.05$) and increases in omissions ($p < 0.01$) and timeout responses ($p < 0.05$) during the OP exposure period, with no significant effects on premature responses, perseverative responses, or response latencies.[61] Decreases in timeout responses continued throughout the washout period, while other deficits corrected.

In a separate study, these researchers also found that rats treated with sub-clinical doses (dose range, 0.25–1.0 mg/kg every other day over the course of 30 days) of DFP had cognitive deficits in spatial learning and recall as well as recognition memory, and that such cognitive deficits may be related to persistent functional changes in brain neurotrophin and cholinergic pathways.[62]

Additionally, a study on the mechanisms underlying the neurological deficits caused by organophosphates by Torres-Altoro and colleagues found that DFP alone or as part of a combination of neurotoxicants caused hyper-phosphorylation of Thr205 tau in mice.[64] Tau functions to stabilize the cytoskeleton, and its hyper-phosphorylation can result in the formation of neurofibrillary tangles and neurodegeneration.[65] Furthermore, phosphorylation at this site is Cdk5-dependent, which plays a critical role in corticogenesis, synaptic plasticity, drug addiction, and cognition.[63]

Malathion

In humans with both acute poisoning and chronic exposure to the organophosphate pesticide Malathion, long-term neurological and cognitive sequelae have been found. Additionally, analysis of population-level data suggests an increased relative risk for aggressive prostate cancer with exposure.

Cognitive Impairments

Recent studies have found neuropsychological deficits among farmers and farmworkers acutely and chronically exposed to Malathion.[66,67] One study looking at farmers from southern Spain, found that both those acutely poisoned with malathion and those with chronic high exposure (>10 years) obtained significantly lower scores on the perceptual, verbal memory, and visuomotor tests than did control subjects.[65] In the case of acutely poisoned subjects, verbal and perceptive learning, and recall and constructive abilities were also impaired.[65] Another study found that the neurobehavioral performance of Hispanic immigrant farmworkers in the U.S. to be lower than that observed in a nonagricultural Hispanic immigrant population.[66] Within the same sample of agricultural workers, there was a positive correlation between urinary organophosphate metabolite levels and poorer performance on some neurobehavioral tests.

Other Illnesses and Conditions

The Agricultural Health Study (AHS), prospective cohort study which ran from 1993-2007, assessed the health of 57,311 licensed restricted-use pesticide applicators and 32,347 applicator spouses for a wide range of conditions.[68] The AHS found no association between chronic malathion exposure and any form of cancer.[67] More recently, however, a review of AHS data by Koutros and colleagues did show a correlation between chronic malathion exposure and aggressive prostate cancer [risk ratio or relative risk (RR) for the highest quartile of exposure (Q4) vs. non-exposed = 1.43].[69] AHS analysis has also shown that physician-diagnosed acute pesticide poisoning and chronic pesticide exposure were associated with depression [odds ratio (OR) = 2.57; and 1.54, respectively].[70]

1.3 LSD, Other Classical Hallucinogens, & Lysergamides

Recent population-level studies of LSD and other classical hallucinogens (psilocybin, DMT, mescaline) have found no long-term negative health effects of use. These findings are in contrast to older case reports that found some long-term cognitive abnormalities (usually flashbacks) associated with use. These results will be discussed in the following section of the report. The literature on the large related-class of drugs called lysergamides does have long-term sequelae associated with them and these are discussed below.

Lysergamides

Cardiac Abnormalities and Valvular Heart Disease

Case reports of cardiac abnormalities and valvular regurgitation events after treatment with a lysergamide abound in the literature.[71,72,73,74] Usually, the drug associated with the heart or valve problems is cabergoline, but bromocriptine, and methysergide, have also been reported as related.[70,71,72,73]

From Tours, France, there is a case report of ST-elevation myocardial infarction (STEMI) reported in a 38-year-old woman a few days after an induced abortion by oral prescription of methylergometrine. Several case reports implicate bromocriptine in the formation of peripartum cardiomyopathy, and includes one from Haiti.[75] Tan, et al., hypothesized that the mechanism for this association between ergot-derivatives and myocardial malfunction was the stimulation of serotonergic (5-HT_{2B}) receptors in the myocardium that caused the development of subendocardial plaques of myofibroblasts and enhanced extracellular matrix formation in the atria and ventricles.[76]

Turning to cases of valvular heart disease, a study in Naples, Italy of 50 Parkinson's disease patients on cabergoline and 50 age and sex matched patients not under treatment with a lysergamide, found that there was an approximately three times higher relative risk to develop moderate tricuspid valve regurgitation in patients with prolactinomas receiving cabergoline therapy than in age and sex-matched healthy controls.[77] Another case report linked aortic valve regurgitation after 12 months of cabergoline therapy in a 57-year old dementia patient.[78]

Tan et al., investigated the frequency of valvular heart disease in a population of Parkinson's disease patients.[75] In that study, seventy-two patients were on bromocriptine, 21 patients were on pergolide, and 47 were control patients. A cardiologist performed blinded transthoracic echocardiographic studies to assess valvular function. The risk for the bromocriptine group to develop any abnormal valvular regurgitation was 3.32 (adjusted odds ratio (OR), 95% CI: 1.11-

9.92, P = 0.03) compared to controls, whereas the risk for the pergolide group was 3.66 (adjusted OR, 95% CI: 1.22-10.97, P = 0.02). When dosage analysis was done, researchers found that patients with a greater exposure to bromocriptine had significantly higher risk of developing both mild and moderate-severe regurgitations (P for trend, 0.005 and 0.019, respectively). This study demonstrated that bromocriptine use was associated with an increased risk of developing valvular heart disease, which occurred in a cumulative dose-dependent manner.[75]

Likewise, a meta-analysis of observational studies on valvular function in Parkinson's patients by De Vecchis, et al., showed that valvular regurgitation of any degree—at one cardiac valve or more —was more frequent in patients who were taking cabergoline compared to those treated with a non-ergot dopamine agonist (DA) agent or to those not treated with any dopamine agonist.[79] The adjusted (inverse variance) odds ratio was 7.25 95% CI: 3.71–14.18; p<0.0001. On the other hand, pooled data from seven studies showed that patients with hyperprolactinemia who were taking cabergoline (n=444) exhibited significantly higher odds of mild- to-moderate tricuspid regurgitation compared to untreated controls (n=954) [adjusted odds ratio (OR) was 1.92 95% CI: 1.34–2.73; p=0.0003.[78]

Interestingly, a study of patients with non-Parkinson's associated hyperprolactinemia showed no increase over baseline of valvular regurgitation or morphology with the start of an average of five years of cabergoline therapy.[80] Moderate valve regurgitation was not associated with the duration of treatment (p = 0.359), cumulative dose of cabergoline (p = 0.173), age (p = 0.281), previous treatment with bromocriptine (p = 0.673) or previous adenomectomy (p = 0.497) in patients with HyperPRL.[79] These researchers note that the mean cumulative dose given their patients was lower than that given Parkinson's patients (279 ± 301 mg), and that their patients tended to be younger than the average Parkinson's patient (41 ± 13 years).[79]

Vascular Insufficiency

Lysergamides have also been linked with severe vascular insufficiencies.[80,81,82] A case report from France found a long stenosis of the right external iliac artery (70%) and a short stenosis (70%-80%) of the left external iliac artery in a 52-year old woman using methysergide to control migraine headaches.[81] The researchers found no other underlying cause of disease that could cause the stenosis. When the lysergamide was removed from her treatment regimen, the stenosis cleared over a 4-month period and remained clear throughout a two-year follow up. A similar case was reported from California and managed with a change of medications [removal of an ergotamine compound (Cafergot)] and endovascular stenting to restore femoral circulation in six weeks.[82] A case of brachial insufficiency from Pakistan due to ergot-derivative ingestion unfortunately resulted in gangrene and amputation was required to clear the secondary infection.[83]

Psychosocial Abnormalities

Lysergamide use is also associated with the onset of a variety of psychosocial abnormalities.[83] Chief amongst these is a significant decrease in impulse control leading to such socially disruptive syndromes as pathological gambling, impulsive eating, compulsive shopping, and hyper sexuality.

One case report discusses the development of compulsive gambling in a young woman more than a decade after she had been treated for a large pituitary tumor.[83] Her treatment included resection to reduce the size of the tumor and bromocriptine to control hyperprolactinemia and prevent tumor regrowth.[84] In 2011 she developed symptoms of compulsive gambling and was treated with behavioral therapy while bromocriptine was tapered off in favor of fluoxetine. A second surgical reduction was also performed. Her symptoms resolved after the bromocriptine was discontinued (8 months after surgery) and she remained symptom free on follow up.[83] A similar case report of compulsive gambling in a woman treated with cabergoline for hyperprolactinemia was also resolved with the withdrawal of the ergot-based dopamine agonist.[85]

Sudden onset of mania and psychosis associated with lysergamide use have also been reported in the clinical literature.[85,86] In all cases, the onset of disease occurs in individuals with no history of this type of disease. In one case a woman developed psychosis complete with auditory and visual hallucinations after three months of treatment with cabergoline for hyperprolactinemia.[86] In the other case, a sudden onset of mania was observed in a woman being treated with cabergoline for amenorrhea.[87] In both cases, the psychosocial abnormalities tapered off with medication change.

1.4 Oximes, Irritants, & Incapacitants

Irritants

CS (Chlorobenzylidene malononitrile)

CS has been associated with long-term respiratory and cutaneous sequelae. Although some of the studies examining these associations have limitations, the evidence is presented below.

Respiratory Symptoms

A Turkish study done on ninety-three men with multiple recent exposures to crowd-control tear gasses, found persistent respiratory symptoms when compared to non-exposed, age-matched controls.[88] Specifically, the National Institute for Occupational Safety and Health (NIOSH) questionnaires administered to study participants showed that more tear-gas exposed subjects (24%) had respiratory complaints (particularly cough and phlegm) for more than 3 months relative to controls (11%).[87] Additionally, spirometric measurements showed that mean forced expiratory volume in one second – forced vital capacity ratio (FEV1/FVC) in smoker-exposed subjects were significantly lower than in smoker-controls ($p = 0.046$). The percent predicted maximal mid-expiratory flow rate (MMFR) in nonsmoker exposed subjects was significantly lower than that in nonsmoker controls ($p = 0.05$). One of the limitations of this study included the inability to determine whether subjects were exposed to CS or OC (pepper spray) or a mixture of the two agents in any of their exposures. Another limitation was that so many of the study participants were smokers, and that this may have predisposed exposed subjects to more severe reactions to CS.[87]

Another recent study taking place in a military setting noted an increased risk for acute respiratory infections after CS exposure in a basic combat training (BCT) cadre.[89] This observational prospective cohort studied the association in 6,723 U.S. Army recruits attending BCT at Fort Jackson, South Carolina from August 1 to September 25, 2012 by capturing and linking the incidence of ARI before and after the mask confidence chamber to CS exposure data. Across the nearly two-month period of the study, recruits had a significantly higher risk (risk ratio (RR) = 2.44; 95% confidence interval = 1.74 - 3.43) of being diagnosed with ARI following exposure to CS compared to the period of training preceding exposure, and the incidence of ARI after CS exposure was dependent on the CS exposure concentration ($p = 0.03$). Assessment of exposures found that all of the soldiers in the training cadre were potentially exposed to doses of CS that exceeded those recommended by the Occupational Safety and Health Administration (OSHA) and NIOSH. Exposure chamber operators were also potentially at risk for a larger than recommended dose.[90]

Importantly perhaps, a study of the effects of CS on detainees of the London Metropolitan Police found that almost one-third (n=36) of the 99 study subjects had a pre-existing medical condition, and that "most" had asthma or mental illness.[91]

In one notable case report of respiratory symptoms subsequent to CS exposure, the subject developed acute laryngeal and bronchial obstruction *three weeks* after being sprayed with CS in a small, police interrogation room.[92] Immediately after being sprayed, she experienced the common CS symptoms of tearing, conjunctivitis, blinking and coughing, but these resolved within a few minutes. Three weeks later, (with no interim symptoms) she presented to the emergency department in acute respiratory distress. A bronchoscopy revealed vocal cord edema and extensive crusting of the glottis, trachea, and bronchi. Two weeks after treatment, a repeat bronchoscopy showed that the bronchi were nearly back to normal, and four months later, her she remained free of respiratory problems. Although the symptoms resolved with treatment, their appearance was delayed after exposure, and as such can be considered a potential sequelae of exposure.

Cutaneous Conditions

A recent case report discussed the development of severe allergic contact dermatitis in a police officer subsequent to exposure to CS.[93] In their report, Barghava and colleagues discuss the case of a 35-year-old policeman who was initially exposed to CS during his police training. After the second or third exposure, during the course of active duty, he developed an eczematous eruption affecting exposed sites, 12–24 hours after exposure.[92] Subsequent exposures, for as little as 3–4 seconds each time, caused more severe cutaneous effects. Examination and a positive patch test confirmed hypersensitivity and allergy to CS. Given that CS exposure is a potential occupational hazard for a member of an urban police force, the officer in the study was placed on disability leave from duty.[9293]

A historical study published in 2005, supports these findings. In this paper, Watson and colleagues reviewed seven cases of police or security personnel who developed moderate to severe skin reactions after CS exposure.[94] Although rashes and erythema can be common symptoms of exposure to CS, they generally resolve soon after exposure. Contrary to this, the patients in Watson's study experienced severe skin problems long after exposure, some of them lasting for months, and a few others that the authors suspect may be permanent. Three of the patients developed an allergic contact dermatitis, necessitating changes in their day-to-day practice: one patient had been transferred to office duties, and another one was able to avoid relapses by wearing protective gloves and mask. Exposure to CS spray seems to have triggered seborrheic dermatitis in one of the patients, and another patient developed a disfiguring leuko-

derma and dysesthesia. Two patients with pre-existing rosacea also showed greater susceptibility to the cutaneous effects of CS, and had subsequent flare-ups of disease for months after exposure.[93]

Incapacitants

302089 & 302582, Butyrophenone derivatives

Although there is no historical or recent technical information available on the specific butyrophenones researched and tested at Edgewood Arsenal in open sources, butyrophenones are still widely used today. Most of the information about toxicology, side-effects, and sequelae are available on haloperidol. These publications were reviewed as part of the literature search and are summarized below.

Movement Disorders

Butyrophenone use is linked to the development of extrapyramidal symptoms such as the dystonias[95,96] and dyskinesias. A meta-analysis by Satterthwaite of 18 trials looked at the relationship between antipsychotic medication use and negative side effects.[96] Using the primary outcome of acute dystonia (N=3,425 total cases), the butyrophenone, haloperidol was associated with 4.7% of all cases.[97] This was significantly higher than the number of cases caused by any of the second-generation antipsychotic medications tested.[96]

- **Dystonia:** A neurological movement disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures. May sometimes resemble a tremor.
- **Dyskinesia:** A category of movement disorders that are characterized by involuntary muscle movements, including movements similar to tics or chorea and diminished voluntary movements. Can manifest as a slight tremor of the hands or an uncontrollable movement of the upper body or lower extremities.

Some of these may be transient and resolve with medication dose adjustment or medication change, and some of these conditions can be long-term and difficult to treat, or even permanent. Some of these movement disorders develop slowly and persist, and are called *tardive* dystonias or dyskinesias.

The prevalence of persistent tardive dyskinesia in a population of 143 patients on conventional antipsychotics (40% of those were on haloperidol) was 5.5% [95% CI: 2.1-11.6]. The link between medication use and serious sequelae was significantly higher for those of butyrophenones, than for patients on other conventional or second-generation antipsychotics.[98]

There is a subset of dystonias that affect the eyes and are called ocular dystonias. When long-term, these dystonias are known as oculogyric crises. Butyrophenones are significantly associated with the risk of developing these disorders.[99] Occasionally, dystonias and oculogyric crises can recur despite the cessation of butyrophenone medications.[100]

Cardiac Abnormalities

In addition to movement disorders, haloperidol is associated with sudden cardiac death.[101] A case-controlled survey of medical practices within a network of 150 general practitioners in the Integrated Primary Care Information project over a six-year period (1995–2001) was performed by Straus and colleagues.[102] In a population of 554 cases of sudden cardiac death, antipsychotic medication use was related to a 3-fold increase in the rate of sudden cardiac death. The risk of sudden cardiac death was also highest among those using butyrophenones (usually haloperidol), those with a defined daily dose equivalent of more than 0.5, and short-term (</=90 days) users.[102] This may be because of the association of many of the butyrophenones with a prolonged cardiac QT interval.[103]

Disruption of cardiac conduction (i.e. length of the QT-interval) can itself be considered a sequelae of exposure because the clinical manifestations of this can be varied and sometimes serious. For example, QT interval prolongation can develop into a cardiac arrhythmia called *torsade de pointes*, which may progress to ventricular fibrillation.[103] One of the most common manifestations is syncope, which can sometimes be accompanied by myoclonic convulsions due to cerebral ischemia.[104]

In addition to their effects on cardiac conduction, antipsychotic medications also have a negative inotropic effect, and reduce cardiac output and severely lower blood pressure.[103]

1.5 Miscellaneous Traditional Chemical Warfare Agents

Table 4. Traditional Chemical Warfare Agents with Potential for Long-Term Sequelae
Sulfur mustard
Phosgene

Sulfur mustard

Between 1980 and 1988, more than 100,000 people are estimated to have been exposed to sulfur mustard gas during the Iran-Iraq War.[105] A significant subset of these sulfur mustard victims (< 30,000 people) have had medical follow-ups, in some cases, for over 25 years post exposure.[106,107] Long-term sequelae have been noted in the skin, eyes, and respiratory systems[108,109] of those exposed, and a wide variety of complaints in the gastrointestinal, endocrine and peripheral nervous systems[110] are also believed to be related to sulfur-mustard exposure. Additionally, genetic alterations, immune dysfunction, neuropsychiatric disorders, and carcinogenesis have been studied.

Sequelae of the Skin

The most common long-term complaints about the skin following sulfur-mustard exposures are of dry skin with persistent pruritus (itching), burning, and desquamation (peeling).[111,112] Those areas of the skin exposed to the gas are also susceptible to chronic eczema and seborrheic dermatitis, with related changes such as skin atrophy, hair loss, and urticaria (hives). In some cases, scarring occurs and has led to contractures and deformity. Vascular changes such as telangiectasia (dilated capillaries commonly called "spider veins") and an increased number of cherry angiomas may be seen.[113]

Changes in pigmentation in and around blistered areas have been noted in up to 55% on those exposed, with hyperpigmentation being more common than hypopigmentation.[114] Pigment changes are believed to be related to the degree of melanocyte injury, and pigment loss appears to be more frequent after exposure to higher doses. A study comparing 500 sulfur mustard exposed Iranian veterans with 500 unexposed veterans,[115] found a higher rate of vitiligo, psoriasis, and discoid lupus erythematous in exposed veterans.

Ocular Sequelae

Acute effects of sulfur mustard include conjunctivitis with dry eyes, pain, and photophobia. However, in most cases, there is a full recovery from these injuries, at least with regard to the restoration of vision to pre-exposure functionality.[105] Nevertheless, a small number of those

exposed to sulfur mustard have corneal scarring or other moderate-to-severe ocular sequelae.[105]

In a study of 112 Iranian veterans exposed to sulfur mustard by Sedghipour and colleagues, the abnormal ocular findings were severe conjunctival vascular tortuosity (65.2%, mean: 13.71 years after exposure), corneal neovascularization (19.6%, mean: 16.54 years after exposure), conjunctival/limbal vessels with ampulliform dilatation (17.9%, mean: 9.33 years after exposure), and delayed keratitis (9.8%, mean: 19.54 years after exposure).[116] Abnormal ocular conditions were significantly more frequent in victims with moderate-to-severe respiratory sequelae.[115]

One of the late-onset conditions that is characteristic of sulfur mustard exposure is ulcerative keratopathy. This sequelae develops in 10 - 15% of those exposed, some 16–20 years after the original injury.[117] The complaints are primarily rapid onset photophobia, lacrimation, and decreased vision. The cause of these changes is not clear, but it is thought to be autoimmune in nature, because of alterations in corneal proteins caused by sulfur mustard.[118]

Respiratory Symptoms

Exposure to sulfur mustard can lead to persistent lung disease, and is the major cause of morbidity in those exposed on a population basis (42% of 34,000 patients).[105] The most commonly reported symptoms are chronic cough, dyspnea (shortness of breath), and increased sputum production.[119] Additional symptoms can include chest pain, gastroesophageal reflux pain, and hemoptysis (coughing up blood).[118]

A study of Kurdish civilians exposed to mustard gas by Iraqi forces has shown that long-term respiratory symptoms are more common in those who had blistering upon exposure.[56] Those with blisters also had decreased lung function as measured by forced expiratory volume in one second (FEV_1) ($p < .0001$).[56]

Historically, a number of respiratory sequelae have been described in those suffering from sulfur mustard exposure and include asthma, emphysema, chronic bronchitis, pulmonary fibrosis, and bronchiolitis. A recent international study by Ghanei and colleagues now suggests that the primary pathological process is actually bronchiolitis obliterans, as determined by the use of high-resolution CT scanning, bronchoalveolar lavage, and open-lung biopsies.[120] Bronchiolitis obliterans involves a chronic scarring process affecting primarily the bronchioles, with progressive loss of these structures and the development of bronchiectasis, and obstructive lung disease.

In addition to lower airway disease, the direct effect of sulfur mustard on the upper airways can lead to damage to the trachea and bronchi. Scarring, fibrosis, and mucociliary malfunction can then lead to stenosis of the bronchi and trachea. Ghazanfari hypothesized that immuno-globulins might play a role in the pathology of the delayed lung symptoms after finding significantly decreased IgM and IgG4 levels in the peripheral blood of mustard-exposed patients.[121] In that study, serum IgM levels also correlated with some measures of lung function (FEV_1) in the mustard-exposed patient group.

Interestingly, genetic polymorphisms may play a role in the development of pulmonary sequelae after mustard gas exposure. A study of 208 Kurdish patients exposed to high doses of mustard gas in 1987 looked at spirometric function and angiotensin-converting enzyme (ACE) genotyping 18 years after exposure.[122] This study found that FEV_1 % predicted tended to be higher in association with the D allele. Specifically, the FEV_1 % predicted was 68.03 ± 20.5%, 69.4 ± 21.4% and 74.8 ± 20.1% for II, ID, and DD genotypes respectively. The ACE DD genotype was overrepresented in the better spirometry group (Chi2 4.9 p = 0.03).

Cancer

A review of the literature on lung cancer and sulfur mustard exposure by Ghanei and colleagues found that, although it is well documented that *prolonged exposure* to mustard gas (even at low doses) was associated with an increased risk of lung or other respiratory tract cancers, evidence, however, is lacking for an association between respiratory cancers and short-term, acute, or single high-dose exposure.[123] The small number of reported lung cancers after single high-dose exposures are too few to determine whether the cancers were due to mustard gas exposure or whether they were caused by confounding factors such as smoking or other environmental exposures.[122]

On the other hand, a small study of 20 lung-cancer patients with single high-dose mustard exposures found a lower than expected age at onset (< 40 years of age) of lung cancer for seven of the patients.[124] Additionally, p53 mutations (within exons 5–8) were predominately G to A transitions; a mutation consistent with the DNA lesion caused by mustard gas.[125] Two of the lung cancers had multiple p53 point mutations, a finding similar to those found in historical studies of lung cancers in Japanese mustard-gas factory workers.[125]

Likewise, a cohort study by Zafarghandi looked at the incidence of malignant disorders in 7,570 Iranian veterans exposed to sulfur mustard and compared that with cancer incidence in 7,595 unexposed comrades in a 25-year follow-up period. This study found that cancer incidence was significantly increased with exposure.[126] All cancer diagnoses were confirmed by pathological

examination, and the most commonly found cancers in both groups (75% of all cancers combined) were lymphatic, hematological, and gastrointestinal. The age adjusted incidence rate ratio was 1.64 (95 % CI 1.15–2.34), and the hazard ratio of cancer was 2.02 (95 % CI 1.41–2.88).[125] An important limitation of this study is that increased contact with healthcare providers in the sulfur mustard exposed group may have led to earlier detection of cancers than in non-exposed controls.

Quality of Life

A small number of studies looked at "soft" or non-medical issues in an attempt to gauge the quality of life of victims suffering from sequelae of mustard gas exposure.[126,127,128] In a study of 242 patients exposed to mustard gas during the Iran-Iraq war, Ebadi and colleagues found that, in general, all those suffering sequelae had a lower quality of life, especially with regard to health factors.[126] These researchers also found that sequelae in three or more systems (i.e. pulmonary, ocular, and skin) were correlated with the lowest quality of life.[127] Another study found that exposed patients with sequelae suffered chronic and prolonged fatigue, but this differed from clinical definitions of chronic fatigue syndromes.[128] The source of fatigue for the people in this study was often the physical sequelae themselves – for instance, fatigue arising from shortness of breath or muscle weakness caused by mustard-gas exposure.[127] These researchers also found the chronic fatigue of physical origin also caused significant fatigue in some patients. Another study found high levels of social isolation and lack of independence, often arising from physical disability, in a group of 17 male veterans exposed to sulfur mustard.[129]

Reproductive Toxicity

There are conflicting reports on the impact of sulfur mustard on fertility.[132] In a study of 81 infertile patients exposed to sulfur mustard during the Iran-Iraq war, Safarinejad found azoospermia and severe oligozoospermia in 42.5% and 57.5% of patients, respectively.[130] They also found a significant decrease in sperm motility in infertile mustard gas-injured patients compared with mean motility according to the WHO criteria for normal ($P < 0.02$). In contrast, Ghanei and colleagues reported that fertility was not adversely affected and suggested that any mustard gas-associated impact on fertility may be latent in nature.[131]

Neuropathic Effects

Neuropathic symptoms are a frequent, yet underreported long-term complication of sulfur mustard exposure.[108] Balali-Mood and colleagues studied 40 Iranian veterans with severe adverse health effects of sulfur mustard exposure.[108] Using electromyography and nerve conduction velocity, they found that 77% of patients had peripheral nervous system abnormalities. Nerve conduction velocity disturbances were more prevalent in the lower extremities than the

upper extremities and more common in sensory nerves than motor nerves. Electromyography revealed a normal pattern for 60% of patients, incomplete interference with normal amplitude in 15% of patients, and incomplete interference with low amplitude in 25% of patients. Disturbances in both upper and lower extremities were mostly symmetric for electromyography and nerve conduction velocity.[108]

Psychiatric Disorders

Mental disorders are frequently reported among the chemically injured veterans. Razavi and colleagues reviewed current literature on the effects of mustard gas on producing mental health disturbances.[132] They found a large percentage of emotional problems (98%), behavioral abnormalities (80%), memory impairment (80%), anxiety (18-65%), low concentration (54%), PTSD (8-59%), and severe depression (6-46%). With less frequency, they found personality disorders (31%), insomnia (13.63%), social performance disturbances (10.73%), thought processing disturbances (14%), seizures (6%), and psychosis (3%).[131]

Phosgene

Individuals who survive exposure and acute symptoms may develop long-term damage to the lungs and increased susceptibility to infection. Sensitivity to irritants may persist, causing bronchospasm, chronic inflammation of the bronchioles and Reactive Airway Dysfunction Syndrome (RADS), a chemically- or irritant-induced type of asthma.[133,134] Follow-up examinations of soldiers who had been exposed to phosgene in World War II found that between 6 to 12 percent of the men had chronic bronchitis, emphysema, pulmonary fibrosis, bronchial asthma or pulmonary tuberculosis.[133]

It is important to point out that symptoms of exposure to phosgene and the potential for sequelae are dose dependent. A survey of phosgene-plant workers in the U.S. recently found that accidental phosgene exposures averaged 8.3 ppm-minutes, ranging up to 159 ppm-minutes with most exposures below 10 ppm-minutes, and that almost a quarter, 24.6%, of the exposed workers reported one or more symptoms within 48 hours of exposure.[135] The most common symptoms were coughing; odd taste in mouth; irritation of eyes, throat, and nose; followed by nausea, headache, and chest tightness.

Most of these symptoms disappeared after a 3-hour period or observation. Only anxiety and "other" symptoms persisted in a few cases after 48 hours. Thirty days after exposure, however, the percentage of workers with symptoms dropped to 1.2%. One exposed worker did develop symptoms of pulmonary edema after two days. He was exposed to 30 ppm-minutes of phosgene. Although unusual, this case demonstrates that there is individual variation in the symptomatology after phosgene exposure. It is also important to note that all of these exposures

(except perhaps the highest, 159 ppm-minutes) would likely be lower than the estimated dose of phosgene received during an offensive attack.[134]

Additionally, in a study of nose-only exposure, adult, male Wistar rats exposed to phosgene for 30 or 240 minutes, showed acute symptoms and histopathological changes for several days after exposure, but no late-onset sequelae 84 days after exposure.[136] The doses administered related to C x t products ranging from 28.2 mg/m3 ×min to 460.8 mg/m3 ×min in the 30-minute exposure group to 47.0 mg/m3 × min to 1008 mg/m3 × min in the 240-minute exposure group. None of the rats died after exposure in either group.

In addition to acute and longer-term injury being dose–dependent, there is a growing body of evidence that suggests that individual variation accounts for difference in injury timing and severity as well – at least in mice.[137] In a recent study by Leikauf, a genetically diverse panel of 43 mouse strains was exposed to phosgene and genome-wide association mapping performed using a high-density single nucleotide polymorphism (SNP) assembly. Of 14 candidate genes previously associated with lung injury or that contained a nonsynonymous SNP within a functional domain, five genes emerged that were associated with acute lung injury: Atp1a1, Alox5, Plxnd1, Ptprt, and Zfand4.[138]

1.6 Environmental Pollutants and Toxic Compounds

Table 5. Environmental Pollutants and Toxic Compounds with Potential for Long-Term Sequelae
Dioxins
Arsenic

Dioxins

Dioxins are associated with neurological, and cutaneous sequelae as well as some cancers. There is also evidence linking dioxin exposure with diabetes, but it is not clear at this time whether this association is causal – so it is not considered sequelae.

Neurological Sequelae

The neurological sequelae resulting from high-dose exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) have been shown to last for decades. For example, a study by Urban and colleagues looked at the neurological function in workers exposed to TCCD in an herbicide plant accident back in the 1960s.[139,140] At the time of exposure, the estimated mean concentration of TCDD was about 5000 pg/g of plasma fat. Only 15 men from the original accident cohort were available for follow-up, despite the exposure of more than 350 individuals and a group of about 80 workers who developed overt signs of poisoning.[138]

The current TCCD plasma concentration for the survivors was 128 pg/g, and researchers found signs of polyneuropathy in nine subjects and confirmed them with neural conduction velocity tests in three men.[138] Fourteen patients had abnormal neural or sensory function tests: 3 had abnormal electroencephalography tests, five had unusual visual-evoked potential, and six had acquired dyschromatopsia. Lastly, single-photon emission computed tomography showed focal reduction of perfusion in various brain locations in all but one patient. Taken together, the survivors test results show that TCDD can damage the nervous system, and that this damage lasts for decades, even after TCDD levels have fallen.[138]

Skin Conditions

Short-term exposure to high levels of dioxins are known to damage liver function and cause chloracne, a chronic inflammatory skin condition characterized by keratinous plugs with cysts and dark acne. Chloracne lesions usually appear on the face, but in case of severe poisoning, they also occur on shoulders, back, chest, and the abdomen. Ukrainian President, Viktor Yushchenko, suffered a very high-profile case of chloracne in 2004, after he was deliberately poisoned with TCDD. When he presented to a hospital after the attack, his serum dioxin level was

108,000 pg/g lipid weight which is about 50,000 times the dioxin level in the general population.[141] Chloracne significantly disfigured his face, leaving scars which will remain for the rest of his life.

Chloracne is not the only long-term sequelae of the skin associated with dioxin exposure. A 24-year follow-up with victims of the Yusho mass food poisoning in Japan found that survivors still had elevated levels of PCBs and dioxin, as well as skin lesions in the same amount and distribution as at the time of the event.[142] A group led by Mitoma categorized and evaluated the specific skin symptoms displayed by 252 of the nearly 14,000 Yusho survivors and compared the severity of their skin symptoms with blood concentrations of the dioxin-like chemical 2,3,4,7,8-PeCDF and PCBs. These researchers found that approximately one-third of Yusho patients still presented with black comedones, acneiform eruptions, and scar formation, and that the prevalence and severity of comedones was worse with advancing age of the subject.[141]

Cancer

In 2007, Zambon and colleagues assessed the role of modelled dioxin levels in the development of 172 cases of visceral and extra-visceral sarcoma registered in the Venice Tumor Registry.[143] The residential history of each subject was reconstructed, address by address, from 1960 to the date of diagnosis and compared with the level of local atmospheric dioxin dispersion for each calendar year. A specific value for exposure was calculated for each address and for each calendar year and expressed as the average of specific time-weighted values. For each sarcoma case, three controls of the same age and sex were randomly selected from population records. These researchers calculated that the risk of developing a sarcoma was 3.3 times higher (95% CI, 1.24 – 8.76) among subjects with the longest exposure period and the highest exposure level. Additionally, a significant excess of risk was also observed in women (OR = 2.41, 95% CI, 1.04 – 5.59) for cancers of the connective and other soft tissues.[142]

Diabetes

In the last few decades, a considerable body of epidemiological evidence has been accumulated that suggest that exposure to dioxin can be considered as a risk factor for diabetes in humans in addition to the traditional lifestyle-related factors, such as excess of energy intake and a lack of exercise.[144,145] Although the evidence for a relationship between dioxin exposure and diabetes is compelling, it is appropriate at this time to consider it an association rather than a causal link.[146] In a review of 72 studies examining the potential connection between diabetes and dioxin exposure, Taylor and colleagues found that there was too much heterogeneity in the studies to perform either a meta-analysis or a pooled analysis. They noted that there seemed to be an overall positive correlation between diabetes and organochlorine compounds, such as trans-

nonachlor, dichlorodiphenyldichloroethylene (DDE), polychlorinated biphenyls (PCBs), and dioxins and dioxin-like chemicals, but that there were too many different diagnostic strategies and approaches to address confounding - particularly of serum lipid levels and the presence of obesity – to allow an analysis to proceed. Additionally, the ages of subjects in the studies was too widely varied to allow confident analysis.[143]

Although the epidemiological data for an association between dioxins and other persistent organic pollutants is equivocal, findings from *in-vitro* and animal studies show that TCDD, PCBs, and other chlorinated POPs can influence insulin signaling,[147,148,149,150,151,152] glucose-stimulated insulin secretion,[153,154,155] and adipocyte differentiation or regulation.[156,157,154] Better designed and implemented epidemiological studies and efforts to align the laboratory work with the epidemiology, along with systematic gap identification is needed in order to see if a causal link exists.

Arsenic

There is a strong body of evidence linking arsenic intake with a variety of health problems, from skin lesions and some cancers, to cardiovascular diseases. There is also an association with metabolic disorders such as diabetes, but it is not clear whether there is a causal link at this time.[158,159]

Skin Conditions

Characteristic early skin problems associated with chronic arsenic exposure are nodular hyperkeratoses (HKs) bilaterally on the palms and soles or interspersed areas of hyper- and hypopigmentation occurring on the trunk or face in a characteristic raindrop pattern. As part of the Health Effects of Arsenic Longitudinal Study (HEALS), Ahsan found that arsenic exposure appears to increase the risk of skin lesions, even at the low end of exposure in this population.[160] Compared with drinking water containing < 8.1 µg/L of arsenic, adjusted prevalence odds ratios for skin lesions was 1.91 for water containing 8.1–40.0 µg/L of arsenic, 3.03 for water with arsenic concentrations between 40.1–91.0 µg/L, 3.71 for 91.1–175.0 µg/L and 5.39 for water with 175.1–864.0 µg/L of arsenic. The HEALS group of researchers also found that males and elderly people are more affected by arsenic exposure, (Ahsan 2006b) as were those with excessive sun exposure,[161] lower nutritional status,[162,163] and lower socioeconomic status (non-land owners).[164,165]

Genetic variability in genes that code for enzymes in arsenic metabolism may also affect individual susceptibility to skin lesions. In a case–control study of 594 skin lesion cases and 1041 controls, the dose–response relationship of skin lesion risk was significantly higher in individuals

with the 677TT/1298AA and 677CT/1298AA diplotypes in the methylenetetrahydro-folate reductase (MTHFR) enzyme (1.66 and 1.77 respectively), than for those with the 677CC/1298CC diplotype.[165] The OR for skin lesions in relation to the GSTO1 diplotype (Glutathione S-transferase 1) containing all at-risk alleles was 3.91.[166]

These early changes in the skin associated with arsenic also predispose to the development of a variety of skin cancers, and a squamous cell carcinoma (in situ) known as Bowen's Disease may also develop.[167] After a latency period that can last years, or even decades, non-melanoma skin cancers, including frank squamous-cell carcinomas and basal-cell carcinomas can also develop.

A small study led by Kathryn Bailey of the U.S. Environmental Protection Agency (EPA) used microarray analysis and qRT-PCR to profile gene expression in hyperkeratotic lesions associated with arsenic exposure.[168] Hyperkeratotic skin samples from seven individuals from Inner Mongolia exposed to high levels of arsenic (212 to 950 ppb arsenic in their drinking water for >20 years), were compared with skin samples from four disease-free people in an urban Mongolian setting. Of the expressed transcripts, 2,824 different transcripts were differentially expressed (up or down regulated) between the HK and control sample groups, with most expression values differing by at least 1.5-fold between the groups. Each of the 9 genes chosen for qRT-PCR analysis demonstrated the same direction of modulation in the HK samples relative to controls as observed in microarrays.[167]

The most commonly altered regulatory genes were roughly grouped amongst indicators of cellular stress, and included components, regulators and effectors of P38, JNK (c-jun N-terminal kinase), and, in particular, the MAPK/ERK pathways[4]. At the cellular and molecular levels, the most significant functions of the modulated genes can be broadly classified into categories involving cell death, cellular development and organization, and cell proliferation. Importantly, apoptosis-related genes are already modulated in the pre-neoplastic HK lesions. In general, perturbations in these processes are thought to be important forces behind the development of arsenic-related non-melanoma skin cancers and other pre-neoplastic and malignant skin diseases.[167,169]

Internal Cancers

The International Agency for Research on Cancer (IARC) has classified arsenic and arsenic compounds as carcinogenic to humans (Group 1), which means that there is sufficient evidence for

[4] The MAPK/ERK pathway is a chain of proteins in the cell that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell, thereby acting as an "on" or "off" switch.

their carcinogenicity in humans.[170] Although less common than the development of skin cancer, arsenic exposure is also associated with internal (visceral) cancers such as those arising in the lungs, liver, kidney, or bladder.[173, 171]

A study of over 3000 lung-cancer patients in Bangladesh found an association between cancer and water arsenic levels of >100 mg/L, with increased risk (OR) being 1.65 (95% CI 1.25 to 2.18). However, this correlation was only seen in smokers exposed to higher levels of arsenic, not in the population at large, and needs further examination.[172]

A study done in the in the Antofagasta area of Northern Chile, where arsenic levels were as high as 800 – 900 mg/L between the late 1950s and the mid- 1970s, but lower thereafter also found a relationship between lung cancer and arsenic exposure.[173] The ORs were 1.00 for < 11 mg/L (reference), 1.27 (95% CI, 0.81–1.98) for 11-90 mg/L, 2,00 (1.24–3.24) for 91-335 mg/L, and 4.32 (2.60 – 7.17) for >335 mg/L.

A meta-analysis of studies by Wang and colleagues examined the risk of liver cancer with arsenic exposure in 12 studies from Asia and Latin America.[174] Arsenic levels between the studies varied widely from 700 to 930 mg/L in Taiwan to 178 mg/L for the high exposure groups in studies done in Argentina. In the studies from Chile, the arsenic levels varied over time with the average arsenic level ranging from 570 mg/L from 1955 to 1969, and decreasing to less than 100 mg/L by 1980. This analysis found the standard mortality ratio of all the studies for the highest and lowest arsenic exposure groups was 1.80 (1.61 to 2.02), indicating an association between arsenic exposure and the development of liver cancer in these studies.[173]

A study examining bladder cancer rates was done in the Antofagasta area of Northern Chile, found that there was an increased risk for bladder cancer as measured by hospital discharges with diagnosis (peak RR 3.6, (95% CI 3.0–4.7)) relative to areas where arsenic levels have always been low.[175] Mortality for bladder cancer was also higher in the arsenic-polluted areas relative to areas of low arsenic, with incident rate ratio (IRR) for men being 5.3 (95% CI 4.8 –5.8) and for women 7.8 (95% CI 7.0–8.7).

Another population-based case–control study in the same area calculated the odds ratios (ORs) for developing bladder cancer relative to quartiles of average arsenic concentrations in the water. The ORs were 1.00 for < 11 mg/L (reference), 1.36 (95% CI, 0.78–2.37) for 11-90 mg/L, 3.87 (2.25–6.64) for 91-335 mg/L, and 6.50 (3.69 – 11.43) for >335 mg/L.[172]

Cardiovascular Diseases

Epidemiological studies have shown that chronic arsenic poisoning through ingestion of arsenic-contaminated water is associated with cardiovascular diseases,[176] including carotid atherosclerosis, impaired microcirculation, prolonged QT interval and QT dispersion. Clinical outcomes associated with arsenic poisoning include hypertension, coronary artery disease, ischemic heart disease, and cerebral infarction. Arsenic-induced cardiovascular diseases in human population may also result from the interaction among genetic, environment and nutritional factors.

High arsenic levels in drinking water (>100µg/L) increased the risk of peripheral artery disease, coronary heart disease, stroke, and carotid atherosclerosis in studies conducted in Chile,[177] Taiwan,[178] Inner Mongolia,[179,180] Bangladesh,[181, 182]and Pakistan.[183,184]

The prospective cohort study from Bangladesh also examined the lower threshold of arsenic concentrations of arsenic in water and found that concentrations above 12 µg/L were associated with an increased hazard of CVD mortality.[181] This study took arsenic samples (urine) from 11,746 men and women and followed the study population for an average of 6.6 years. During the course of the study, 198 people died from diseases of circulatory system, accounting for 43% of total mortality in the population. The mortality rate for cardiovascular disease was 214.3 per 100 000 person years in people drinking water containing <12.0 µg/L arsenic, compared with 271.1 per 100 000 person years in people drinking water with ≥12.0 µg/L arsenic.[181]

Looking more closely at the relationship between arsenic and mortality from ischemic heart disease (IHD), these researchers found that after adjusting for confounding factors, there was a dose-response relationship between exposure to arsenic in well water assessed at baseline, and mortality from ischemic heart disease and other heart disease. The hazard ratios for IHD mortality relative to arsenic concentration in well water were 1.00 for concentrations of 0.1-12.0 µg/L (reference value); 1.22 for concentrations of 12.1-62.0 µg/L; 1.35 for 62.1-148.0 µg/L; and 1.92 for 148.1-864.0 µg/L (p=0.0019 for trend).[181]

Another study followed 280 men and 355 women for 17 years in an area of southwest Taiwan with a high prevalence for potential arsenic poisoning.[185] Before the mid-to late 1970s, water for drinking or cooking was drawn from artesian wells having extremely high arsenic concentrations of 700 – 930 µg/L. A tap-water system was implemented in the 1970s, and after this time, water for drinking or cooking came from the tap. Estimated lifetime cumulative arsenic exposures were obtained by multiplying the median arsenic level in a specific village by the duration of drinking artesian well water in the village, and summing the values across the period subjects lived in the arseniasis-endemic area.[184]

This group found that high cumulative arsenic exposure was significantly associated with QT-dispersal (QTD), indicating a lack of ventricular repolarization homogeneity, and that this relationship varied in a dose-dependent manner ($p < 0.001$). After adjusting for potential confounders, they also found a significant association of QTD with coronary artery disease and carotid atherosclerosis. Furthermore, the hazard ratio for cumulative cardiovascular mortality was 3.9 (2.1-6.2, p=0.002) for QTD > 65 ms.[184]

Researchers have long observed the individual variability in susceptibility to arsenic toxicity, and have hypothesized that this may be due in part to differences in age, sex, and arsenic metabolism.[186] Additionally, within the last two decades, the genes coding the enzymes responsible for arsenic metabolism have been cloned and characterized. Building on these two developments, a recent study from Taiwan investigated the possible contribution of genetic factors to the development of cardiovascular after long-term arsenic exposure.[187]

This study, by Liao and colleagues, examined variations in PON1, PON2, (human paraoxonase encoding genes) and AS3MT and GSTO (arsenic metabolism genes), and found that arsenic exposure was significantly correlated with any ECG abnormality (representing a range of clinical conditions from myocardial infarction or ischemia to arrhythmias to prolonged QT wave and ventricular repolarization abnormalities). Furthermore, polymorphisms in PON1 and PON2 (PON1 Q192R, -108C/T and PON2 C311S) were associated with the incidence of ECG abnormality and CVD risk. Although it is unclear why polymorphisms in the PON1 and PON2 gene families should be related to increased risk, the researchers hypothesized that since PON1 products can prevent both HDL and LDL oxidation, it is therefore protective against the development of some Cardiovascular diseases.[186]

Diabetes

Evidence for a link between arsenic exposure and diabetes is equivocal, with some studies finding an association and others not. The lack of agreement between studies remains regardless of whether diabetes is measured by existing diagnosis, medical support for symptoms, blood tests, oral glucose tests, or diabetes mortality. A recent, population-based examination that took place as part of the HEAL study in Bangladesh also found no association between arsenic exposure and diabetes.[188]

In this study, more than 90% of the 11,319 cohort members were exposed to drinking water with arsenic concentration < 300 µg/L. The adjusted odds ratios for diabetes in relation to quintiles of time-weighted, arsenic concentrations in water were 1.00 for concentrations of 0.1–8 µg/L (reference), 1.35 (95% CI, 0.90 – 2.02) for 8–41 µg/L, 1.24 (0.82–1.87) for 41–91 µg/L, 0.96

(0.62–1.49) for 92–176 µg/L, and 1.11 (0.73–1.69) for concentrations above ≥ 177 µg/L. Furthermore, no relationship was found in this study between arsenic exposure and diabetes when urinary concentrations of arsenic were measured instead of those in drinking water. HEAL researchers also observed no association between arsenic exposure and prevalence of glycosuria and no evidence of an association between well water arsenic, total urinary arsenic, or the composition of urinary arsenic metabolites and glycosylated hemoglobin level (HbA1c).[187]

1.7 Antibiotics

Table 6. Antibiotics with Potential for Long-Term Sequelae
Chloramphenicol
Tetracycline

Chloramphenicol

The most serious long-term sequelae of chloramphenicol use is the development of aplastic anemia, or depletion of blood cells, which, if it develops, usually occurs weeks or months after antibiotic treatment has ceased. It is a relatively rare sequelae, but is included as a potential long-term sequelae because the evidence for an association is strong. There is no way to predict which patients will develop anemia, although genetic polymorphisms predisposing some individuals are believed to be involved.[189]

Additionally, some historical case-control studies link chloramphenicol use to the development of leukemia, which in many cases is diagnosed after aplastic anemia.[188] The risk of leukemia is higher with longer chloramphenicol treatment periods. It is possible that children are more likely to develop leukemia after chloramphenicol use than adults, as the relationship in studies with child subjects is usually stronger than it is in studies on adults.[188]

Chloramphenicol use is also associated with bone-marrow suppression and optic neuritis,[190 191] but these conditions resolve after the antibiotic is withdrawn and are not associated with long-term sequelae.

Tetracycline

Tetracycline antibiotics are associated with a number of acute adverse effects including drug-induced systemic lupus erythematosus,[192] photo-onycholysis,[193] and esophageal scarring.[194] However, all of these symptoms and syndromes resolve when drug therapy ceases, and exposure does not cause long-term sequelae. A case of renal failure as a result of tetracycline use has been reported, but the patient had pre-existing polycystic kidney disease as an underlying condition.[195]

A recent retrospective cohort study, however, found a possible association between the tetracycline-class antibiotic use and the onset of inflammatory bowel disease (IBD), ulcerative colitis and Crohn's Disease.[196] In this study, Margolis and co-workers looked at the association in over 94,000 individuals using The Health Improvement Network database of the United Kingdom.

They calculated the hazard ratio (HR) for developing IBD subsequent to any exposure to a tetracycline antibiotic to have been 1.39 (95% CI: 1.02, 1.90). HRs for individual antibiotics were 1.19 (95% CI: 0.79, 1.79) for minocycline, 1.43 (95% CI: 1.02, 2.02) for tetracycline / oxytetracycline, and 1.63 (95% CI: 1.05, 2.52) for doxycycline. For ulcerative colitis, the associations (HR) were 1.10 (95% CI: 0.76, 1.82) for minocycline, 1.27 (95% CI: 0.78, 2.07) for tetracycline /oxytetracycline, and 1.06 (95% CI: 0.53, 2.13) for doxycycline. For Crohn's disease (CD), the associations (HR) were 1.28 (95% CI: 0.72, 2.30) for minocycline, 1.61 (95% CI: 0.995, 2.63) for tetracycline / oxytetracycline, and 2.25 (95% CI: 1.27 4.00) for doxycycline. These increased HRs remained even after robust sensitivity analyses of potentially confounding factors, such as gender, age, use of oral contraceptives, and cigarette smoking.[195]

It is unclear why the use of tetracycline antibiotics would cause inflammatory bowel disease or Crohn's Disease in some individuals, but alterations in gut flora, gut cellular activity, or T-cell activity due to antibiotic use might be involved.[197, 198]

1.8 Miscellaneous Other Compounds

PABA

Several recent studies link exposure to PABA with the development of photoallergic contact dermatitis (PACD). PACD is a delayed type IV hypersensitivity reaction. Although its exact prevalence is not known because it varies between populations, PACD was reported in only 2 to 10 percent of patients tested for photo allergy in North America and Europe, respectively.[199,200,201] A Chinese study by Gao and colleagues, however, found PABA-related PACD in 14.7% of 2,454 patients photo patch tested.[202] This variation could be related to PABA being used more frequently in Chinese cosmetics than in products marketed in North America and Europe.

Although uncommon, PACD can cause significant long-term morbidity in some patients that may require major lifestyle changes among those afflicted. Chronic or recurrent PACD can continue for months or years after exposure to the sensitizing substance. Secondary infection of the allergic rashes can occur, and eczema can develop.

Oral administration of PABA rarely results in an acute but poorly defined systemic illness that can include fever, myalgia, muscle weakness, rash, and eosinophilia (DRESS). However, when dosing stopped, the symptoms abruptly resolved and did not return,[203,204] Thus, DRESS should be considered an adverse reaction to PABA, not a long-term sequelae.

2.0 Agents and Substances with Little or No Evidence for Long-Term Sequelae

2.1 Classical Biological Agents and Vaccines

Table 7. Biological Agents with No Evidence for Long-Term Sequelae
Francisella tularensis **(tularemia)**
Plasmodium vivax **(vivax malaria)**
Staphylococcal Enterotoxin B (SEB)
Pseudomonas Endotoxin
Sandfly Fever, Sicilian Strain
Typhoid Fever
Rickettsia rickettsii **(Rocky Mountain Spotted-Fever)**
Plague Vaccine
Adenovirus Vaccine, live
Yellow Fever 17-D Vaccine
Rift Valley Fever Virus Vaccine
Chikungunya Virus Vaccine

Francisella tularensis (Tularemia)

The literature on short or long-term sequelae to *tularensis* infection is very sparse. This is possibly because of tularemia's polymorphic presentation that depends upon the route of infection. Cases studies of unusual symptoms during or following active infection were found, but there were no population-based studies describing disease sequelae. The case studies included cutaneous (erythema nodosum),[205] immunological (Sweet's Syndrome), vascular (endocarditis)[206] and neurological (tularemic meningitis, with or without cerebral abscesses)[207,208,209] symptoms. These illnesses can be severe, but they are primary presentations of disease following infection, or complications of infection, not post-infection sequelae.

Only one case report was found, however, that discussed a long-term sequelae to tularemia. Ylipalosaari and colleagues discussed the neurological disorder reported on a patient who developed serious Guillain–Barré polyneuropathy following ulceroglandular tularemia infection.[210] This patient was a 38-year old man who presented with fever and muscle weakness that progressed to admission to an intensive care unit, paralysis in the upper and lower extremities, and mechanical ventilation. He was treated with multiple antimicrobial medications and plasmapheresis, and returned to work 9 months after hospital admission. Although serious, and long-

lasting, because this association between *F. tularensis* and Guillain-Barré is only based on one case study, it is not included in this analysis.

Plasmodium vivax (Vivax Malaria)

Although traditionally viewed as a milder malaria infection, case reports of sometimes severe complications of *P. vivax* malaria have been increasing in the literature over the past decade. A review and assessment of the scientific literature shows that complications of vivax malaria include a variety of neurological symptoms including tremors or neuropathy,[211,212,213] and renal dysfunction. These symptoms and syndromes do not count as long-term sequelae because they resolve spontaneously or with treatment within weeks or months after appearance.

Neurological Impairments

Post-malaria neurological syndrome (PMNS) is defined as the acute onset of neurological or neuropsychiatric syndrome in patients who had recently recovered from malaria and have negative blood film at the time of onset of neurological symptoms.[214] This distinguishes it from cerebral malaria, which occurs during the period of parasitemia in *P. falciparum* infection. The time from eradication of systemic parasitemia to the development of this syndrome can be up to nine weeks.[213] There is a 0.12% prevalence of PMNS in patients with malaria and it is 300 times more common in patients with severe malaria compared to those with uncomplicated malaria.[213]

Reported clinical features include convulsions, confusion, psychosis, tremors, cerebellar ataxia, motor aphasia, and generalized myoclonus.[213] Two recent case reports of neurological deficit following *P. vivax* infection fits within the post-clinical spectrum of PMNS. Kohar and colleagues described a case report of a bilateral facial palsy that presented two weeks after *P. vivax* infection and spontaneously resolved after four weeks.[213] Lampah and colleagues reported a case in which a child presented with severe tremor after resolution of *P. vivax* induced coma.[215] The tremor had improved but was still present at the time of hospital discharge.

Another type of neurological disorder reported in the literature includes acute disseminated encephalomyelitis (ADEM). A case report by Goyal and colleagues shows ADEM developing after the resolution of malarial infection in a young girl.[216] After her initial (smear-negative) discharge, the child was readmitted to hospital feverish and unconscious. After the ADEM diagnosis and treatment with corticosteroids, she regained consciousness but took almost six months to begin to walk again.

Renal Complications

Several cases in the literature report long-term disability resulting from acute kidney injury during active *P. vivax* infection.[216,217] Kute and colleagues published a report in 2012 from India that discussed a case of severe renal cortical necrosis which left the patient on hemodialysis and an assessment of stage 4 chronic kidney disease on five-month follow up.[217] Keskat et al., described another case, also from India, that resulted in only partial restoration of renal function after acute failure, possibly from hemolytic uremic syndrome.[218]

These conditions are not included in this analysis because they resolve – with treatment – after the parasite has cleared, or because they are still only represented in a couple of case reports and the association is not strong at this time.

Staphylococcal Enterotoxin B (SEB)

There were no specific long-term sequelae reported in the scientific literature for SEB intoxication. However, acute intoxication with SEB-producing *S. aureus* is associated with some severe inflammatory complications, including toxic shock syndrome.[220] Generally, shock subsides as infecting bacteria and toxins are cleared from the body, but damage to organ systems may persist for weeks or months following exposure.[220] Likewise, chronic carriage of toxin-producing strains may also be linked to select inflammatory disease states.[223]

Toxic Shock Syndrome (TSS)

Staphylococcus enterotoxin B and other *S. aureus*-derived toxins are known causes of TSS, as are other viral and bacterial pathogens. Unlike other antigens, SEB activates CD4+ and CD8+ T-cells directly, which in turn increases the production of pro-inflammatory and anti-inflammatory cytokines.

A recent DNA-microarray analysis of SEB-infected HLA-DR3 transgenic mice, Rajogopalan and colleagues found that the genes producing interleukin-6 (IL-6) was upregulated 700-fold, while the genes producing interferon-gamma (IFN- γ) and IL-2 were upregulated 360-fold and 240-fold respectively.[219] Although the gene expression (production) of these cytokines was greatly increased, the expression of the genes coding for their receptors was increased only slightly or in some cases decreased. Similar dysregulation of other cytokines, chemokines and proteases also occurred.[218] Modelling of the effects of the subsequent organ and tissue damage predicted significant damage to the liver and kidneys – hallmarks of the onset of toxic shock.

Another recent study by Tilahun and colleagues has also elucidated the role of IFN- γ in the severity of SEB-induced TSS.[220] This study found that lethality of TSS in HLA-DR3 transgenic mice

was related to IFN- γ mediated intestinal pathology. Specifically, high levels of IFN- γ increased small-bowel permeability to macromolecules.[219]

So, although there are no publications in the literature describing the long-term health effects of acute SEB intoxication at this time, the mechanisms for longer-term cytokine dysregulation as a result of SEB-induced TSS may continue to produce sub-clinical illness for some time after toxin and bacteria have been cleared.

Inflammation

Chronic carriage of toxin-producing *S. aureus* has also been implicated in the development of specific inflammatory pathologies, namely food allergy[221] and the development of nasal polyps.[222,223] Although these low-level inflammations do not produce a great deal of morbidity, and seem inconvenient rather than dangerous, these disease processes may be indicative of other sub-clinical sequelae produced after exposure to SEB.

Pseudomonas Endotoxin

As with *Staphylococcus aureus* enterotoxin-B, there is little on the specifics of long-term health effects resulting from the exposure to *P. aeruginosa* endotoxin. However, the lipopolysaccharide (LPS)-derived endotoxin is implicated in a number conditions or diseases ranging from severe (major depression)[224] to more mild manifestations such as osteolysis[225] in chronic otitis media.

Major Depression

Recent studies have provided evidence that major depression is accompanied by an activation of the inflammatory response system and that pro-inflammatory cytokines and LPS may induce depressive symptoms (e.g. fatigue, autonomic and gastro-intestinal symptoms, and a subjective feeling of infection).[223] For example, Maes and colleagues examined the serum IgM and IgA against LPS of enterobacteria, and found that they were significantly ($p=0.0002$ for IgM and $p=0.01$ for IgA) greater in depressive patients (12/28 for IgM and 11/23 for IgA) than in normal volunteers (0/23 for IgM and 2/23 for IgA).[223] Specifically this study found that the IgM against *P. aeruginosa* and *P. putida* LPS was much higher in depressive patients than in controls. Increased translocation of LPS across the gut can also account for depression in alcoholics and potentially in other diseases related to gut permeability, such as inflammatory bowel disease and some autoimmune disorders.[223] It is unclear at this time whether LPS translocation occurs first, and is followed by an inflammatory response (notably increases in IL-6 and IFN-γ), or whether an inflammation increases gut permeability and secondarily moves LPS across the gut.

Osteolysis

There is a delicate balance between bone deposition and absorption in healthy individuals: osteoblasts lay down bone and osteoclasts resorb it.[224] In some disease states such as chronic otitis media, *P. aeruginosa* has been implicated as a cause of increased osteoclastic bone resorption sometimes leading to hearing loss, vertigo, and facial paresis. A recent murine study by Nason and colleagues, demonstrated that *P. aeruginosa* LPS can indeed cause turn precursor cells into mature osteoclasts.[224] Furthermore, LPS stimulated the production of tumor necrosis factor-alpha (TNF-α), IL-1α, and IL-6, all of which subsequently promote osteoclast formation in an autocrine - paracrine manner. The authors of this study speculate whether this mechanism may also be involved in the formation of multinucleated giant cells seen in other chronic inflammatory states.[224]

Sandfly Fever, Sicilian Strain

Because the Sicilian Strain of Sandfly fever produces a relatively mild illness (it is also known as the 3-Day Fever) relative to other *Phleboviruses*, there is no evidence in the literature of long-term health effects associated with infection.[226]

There is one recent case report of encephalitis resulting from infection with Turkey virus which has only recently been considered something more than just a variant of Sicilian virus.[227] The case is notable because on two-month follow up, the patient, a 63-year old woman, was left with cognitive disturbances and unable to walk without assistance.[226]

Typhoid Fever

There are a number of complications associated with typhoid fever that include neurological impairments such as nerve palsies and weaknesses, and Guillain-Barré Syndrome. These, are complications of infection rather than long-term sequelae, because they resolve, spontaneously or with treatment, within a few weeks or months after infection and do not reoccur.

Neurological Impairments

Neurological complications of typhoid fever are not uncommon, with reported neurological complications including encephalopathy, spastic paralysis of cerebral origin, convulsions, meningitis, Parkinsonian syndrome, and sensory motor neuropathy.[228] Several recent case reports from Asia and the Pacific Rim (Fiji) have also noted Guillain-Barré Syndrome as a long-term health effect of typhoid fever.[229, 230, 231] These three case studies were all pediatric patients, however, and the time to resolution of the long-term symptoms of Guillain-Barré varied widely from two weeks to three months.

Facial and palatal neuropathy and other cerebral nerve palsies following typhoid fever have also been reported. Joshi et al., described two recent case studies from India in which symptoms of palatal palsy completely resolved within five to seven weeks.[227]

In 2013, Talukdar also reported a case of mixed catatonia and Parkinsonism as sequelae to typhoid fever in an 18-year old man.[232] This case, although severe, and included periods of total paralysis, resolved with appropriate treatment four weeks after hospital discharge. The mechanism by which typhoid fever may produce neurological illness is still unknown, but it is possible that *S. enterica*, var. Typhi endotoxins (LPS) transiently interfere with cholinergic–dopaminergic control of the basal ganglion producing Parkinsonian rigidity.

Abdominal Complications

Sequelae can also arise from complications of the infection in the abdominal organs and include the long-term effects of pancreatitis, gallbladder disease, and bowel perforation.[233,234,235] These sequelae, although sometimes severe, tended to resolve several weeks or months after the infection is cleared. [233] Surgical removal of gangrenous gallbladder and repair of intestinal perforation were also necessary. Case reports also implicate *Salmonella enterica*, var. Typhi in the development of gallbladder cancer, although this association is still somewhat controversial.[236]

***Rickettsia rickettsii* (Rocky Mountain Spotted-Fever)**

Complications (not sequelae) following acute Rocky Mountain spotted fever are largely neurological in origin and include partial paralysis of the lower extremities, hearing loss, loss of bowel or bladder control, or movement disorders, and language disorders.[237] Complications of myocarditis subsequent to RMSF infection have also been noted. Both the neurological and the vascular sequelae resolved with proper treatment several weeks after discharge.[238]

Plague Vaccine

None of the plague vaccines currently or recently in use are associated with long-term sequelae. There are a few short-term complications associated with some of the vaccines, but these are generally mild and transient. The live plague vaccine (EV76) created in the 1920s in the Soviet Union to immunize plague workers and populations at risk is highly reactogenic and produces a number of local and systemic, vaccine-related side effects, such as extreme pain at the injection site, swelling, local erythema, regional lymphadenopathy, malaise, headache, giddiness, anorexia, weakness and mild fever with an elevated body temperature of up to 38.5–39.5 centigrade.[239]

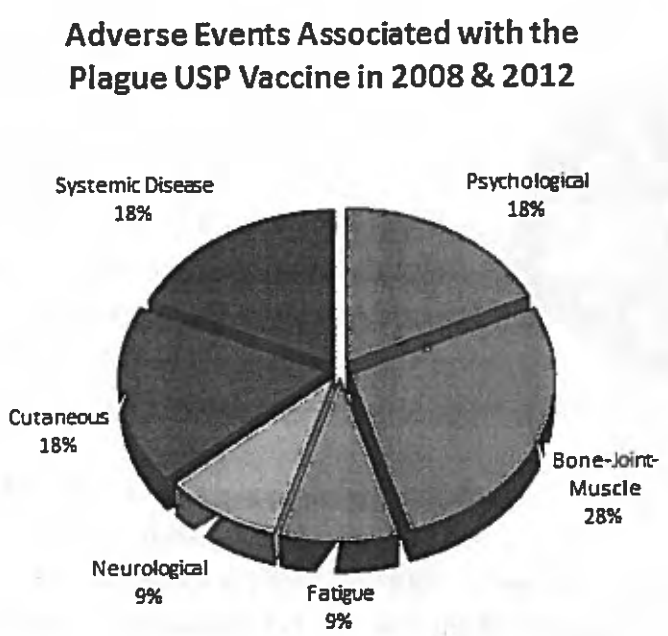


Figure 3. Adverse Events in the Plague USP Vaccine, 2008 & 2012. (Data: CDC Vaccine Adverse Events Reporting System)

The Plague USP vaccine is a formaldehyde-killed preparation of the highly virulent 195/P strain of *Y pestis* and was once licensed in the U.S.[238] Incomplete protection (it protected against cutaneous but not aerosol challenge) lead to its use being discontinued. *Self-reported* complications from administration of plague USP vaccine have been collected by the Centers for Disease Control and stored in the Vaccine Adverse Events Reporting System (VAERS).[240] The most commonly reported VAERS complications include cutaneous discomfort at the injection site, bone-joint or muscle pain, psychological problems or systemic disease (See Figure 3.)

Adenovirus Vaccine, live

The new adenovirus vaccine used by the U.S. Department of Defense has few complications and no sequelae associated with its administration. Phase I trials of this vaccine showed it to be well tolerated, with only five severe adverse events reported, and none of them were determined to be related to the vaccine.[241] Phase III trials of this vaccine also found it to be safe, and serious adverse events were documented in only 1.2% of vaccine recipients and 1.2% of placebo recipients. The most common adverse events were headache, upper respiratory tract infection, and arthralgia.[242]

Yellow Fever 17-D Vaccine

Yellow fever, which occurs in tropical South America and Africa and has been successfully controlled in many areas by using the live, attenuated yellow fever 17D vaccine developed in 1936.

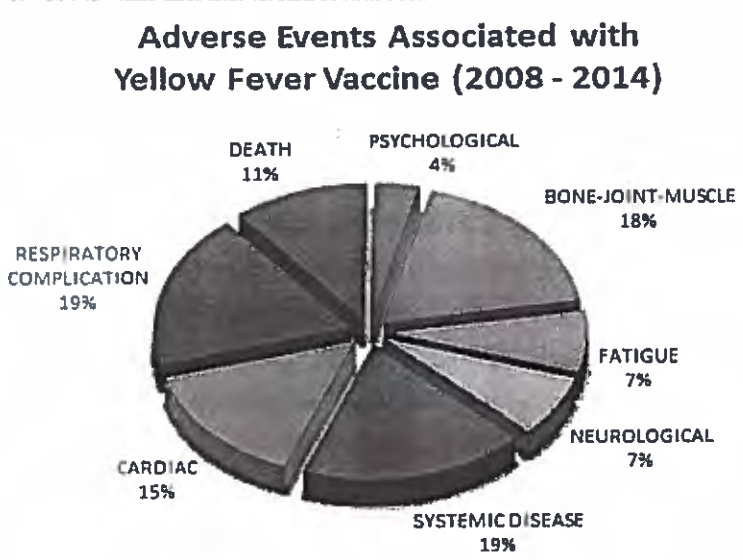


Figure 4. Adverse Events Associated with Yellow Fever Vaccine, 2008 -2014 (Data: Vaccine Adverse Events Reporting System, CDC)

Serious adverse events, including death, have however been associated with the vaccine in several countries, including the United States (See Figure 4.)[243,244] Even if severe, these are complications of vaccination and not sequelae.

Between March and April of 2001, 309,920 doses of dramatic Yellow Fever 17D vaccine were administered in a mass vaccination campaign in Juiz de Flora, Brazil. A rise in reporting of adverse events followed the campaign with symptoms ranging from fever and myalgia to jaundice and aseptic meningitis were reported.[245]

In 2001, a new syndrome, yellow fever vaccine-associated viscerotropic adverse events (YEL-AVD) was reported.[246] The pathogenesis of this adverse event involved unchecked replication of vaccine virus in visceral organs. The reported incidence of YEL-AVD approximates 0.4 per 100,000 vaccinations.[245] From 1990 to 2012, the number of cases of YEL-AD (n = 31) and deaths (n = 12) from YEL-AVD in travelers has exceeded the reports of YF (n = 6) acquired by natural infection.[247] This raised the question whether the risk of vaccination exceeded the benefit in travelers.[246]

Rift Valley Fever Virus Vaccine

There are no reports of long-term sequelae associated with vaccines against Rift Valley Fever Virus. Immunization side effects of early formalin-killed vaccines, NDBR 103 and TSI-GSD 200, in human volunteers were reported to be local reactions, such as erythema, swelling, tenderness or pain at the site of injection. No specific febrile reaction or severe adverse effects related to the vaccination were reported, except for one case of Guillain-Barré syndrome, which might have been due to enterovirus infection.[248]

Because inactivated vaccines require multiple booster shots to protect against wild-type infection, live, attenuated vaccines were developed. One candidate, MP-12, was tested on human volunteers and has been shown to be safe and immunogenic when an adequate dose was administered. This vaccine is currently undergoing further Phase II clinical evaluation.[249] Other vaccines for RVFV include recombinant proteins, virus-like-proteins, DNA vaccines and plasmid vaccines are also under development but have not yet been tested on humans in phased clinical trials.[250]

Chikungunya Virus Vaccine

There are no long-term sequelae associated with vaccines formulated against Chikungunya Virus. The first Chikungunya vaccines were formalin-inactivated vaccines prepared from a variety of cell substrates including African green monkey kidney, mouse brains, and chick embryo cells. The vaccine made from chick embryo cells did not elicit a potent immune response. However, vaccines made from the other two materials did with no adverse events in human volunteers.[251] Likewise, a live-attenuated CHIKV vaccine candidate (strain 181/clone25) was tested in Phase I trials and found to be safe and well-tolerated. It produced a transient arthralgia in some patients in Phase II and development was discontinued.[250]

More recently, a safety and tolerability trial in 2012-2013 of a virus-like particle (VLP) Chikungunya virus vaccine, VRC-CHKVLP059-00-VP, at the National Institutes of Health in Bethesda, MD found no serious adverse vaccine-related events in the study population.[250] Overall, nine (36%) of 25 participants reported mild local reactogenicity, whereas ten (40%) reported mild systemic reactogenicity at least once after a vaccination. There were no reports of arthralgia after vaccination.

2.2 Anticholinesterases

Table 8. Anticholinesterases with No Evidence for Long-Term Sequelae
Soman (GD, EA 1210)
Cyclosarin (GF, EA 1212)
GV (GP, EA 5365)
VX (EA 1701)
Other V-agents (VE, VG, VM)
Physostigmine (CAS 57-47-6)

Soman (GD, EA 1210)

Anxiety is a long-term sequelae of soman exposure is discussed in the previous section of this report. Here, the short-term neurological and cognitive effects are summarized.

Neurological and Cognitive Impairment

Soman-induced seizures cause neuronal damage in brain limbic and cortical circuits leading to persistent behavioral and cognitive deficits. One common type of consequence of soman –induced seizures in rats is an elevated startle response, sometimes accompanied by altered sensorimotor gating.[252] Soman exposure can also impair fear conditioning in rats, with soman- exposed animals spending less time freezing than controls, possibly due to the neuropathy observed in the hippocampus, amygdala, and thalamus.[253]

Filliat and colleagues found that mice exposed to 1.2 LD_{50} of soman (110 mg/kg in 200 ml of saline solution) could be divided into high-weight loss (HWL) and low-weight loss (LWL) groups, and that this grouping was predictive of neuropathological damage to the hippocampus.[254] Initially, both groups of mice showed a decrease in their motor performance subsequent to an acute soman toxicity phase. Then, total motor recovery occurred for the LWL group.

Comparatively, HWL mice showed only transient recovery prior to a second decrease phase due to soman-induced delayed toxicity.[253] One month after intoxication, mnemonic cognitive performances of the LWL group were similar to controls while the HWL group did not exhibit any learning skill.[253] Three months after poisoning, compared to controls, the LWL group showed similar mnemonic performances in the maze test but a mild deficit in the Morris water maze task. At the same time, learning skills slightly recovered in the HWL group.

Cyclosarin (GF, EA 1212)

Unlike other G-Series anticholinesterase agents, animal studies with subclinical doses of cyclosarin have found no evidence for long-term sequelae. There are, however, some short-term neurological and cognitive complications of exposure that are transient and resolve in a few weeks' post-exposure.

For example, a study of the effects of sub-clinical inhaled doses of cyclosarin in rats, Genovese and colleagues found that the largest concentration (5.2 mg/m^3) of cyclosarin disrupted performance on a variable food-reinforcement task that the animals had been taught (and successfully performed) prior to exposure. This deficit, however, resolved by the third post exposure test session, and remained resolved across 11 weeks of behavioral testing. These results suggest that subclinical doses of cyclosarin may produce performance deficits in learned behaviors, but that the deficits appear to be transient.[255, 256]

GV (GP, EA 5365)

No information in the English language was found on the long-term sequelae resulting from GV exposures.

VX (EA 1701)

There was no evidence found for long-term sequelae associated with VX exposure. However, animal studies have found several types of acute injury (neurological and cognitive as well as respiratory) in survivors of VX exposure, but these injuries resolve and do not return.

Neurological and Cognitive Impairment

In a study on repeated sublethal exposures to VX, Myers and colleagues found that performance of a learned differential reinforcement task was impaired in rats given larger exposures (0.4 LD_{50} and 0.5 LD_{50}) of agent.[257] These researchers found, however, that performance of tasks returned to normal one-week after exposure and remained stable for the remainder of the test period.[256] This suggests that damage from sublethal doses of VX is transient in small animals. Bloch-Shilderman and colleagues also noted transient damage with repeated sublethal doses (2.25 µg/kg/day, 0.05 LD_{50} for 3 months) in rats.[258]

Pizarro and colleagues found that subsequent to repeated sublethal exposures to VX, (0.2 LD_{50} and 0.4 LD_{50}) brain-derived neurotrophic factor (BDNF) messenger RNA expression was significantly elevated in multiple brain regions in mice ($p < 0.05$), including the dentae gyrus, CA3, and CA1 regions of the hippocampal formation, as well as the piriform cortex, hypothalamus, amyg-

dala, and thalamus.[259] Seventy-two hours after the last exposure, however, BDNF was only increased in the CA3 region of the hippocampus. This is significant because neurotrophins in the hippocampus also contribute to long-term potentiation, learning, and memory.[258]

Likewise, using microarray analysis, Gao found that marked changes in gene expression in cultured human neural cells 6, 24, and 72 hours after exposure to 0.1 or 10 µM of VX for 1 hour.[260] Gao noted that "functional annotation and pathway analysis of the differentially expressed genes has revealed many genes, networks and canonical pathways that are related to nervous system development and function, or to neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, and Parkinson's disease." Specifically, these researchers found that the neuregulin pathway was impacted by VX exposure, and that this has important implications in many nervous system diseases including schizophrenia.[259]

Respiratory Impairment

A study done at the Walter Reed Army Institute of Research has demonstrated that inhalation exposure of VX (dose of 50.4 to 90.4µg/m3 for 5 min. or 0.5 LD_{50} to 0.9 LD_{50}) causes lung injury in guinea pigs.[261] Specifically, Wright and colleagues found that the pulmonary damage induced by VX has the classic signature of acute lung injury, including increased inflammatory cell infiltration, decreased macrophage/monocytes, increased protein in bronchoalveolar lavage fluid, and pulmonary edema.[260]

Other V-agents (VE, VG, VM)

There was no information about long-term health effects of the other V-series agents.

Physostigmine (CAS 57-47-6)

No publications could be found that provided evidence for any long-term sequelae associated with physostigmine exposure.

2.3 Anticholinergics

Table 9. Anticholinergics with No Evidence for Long-Term Sequelae
3-Quinuclidinyl benzilate (BZ, QNB)
Tox Number B002: N-Methyl-4-piperidyl cyclopentylphenyl glycolate
Tox Number B003: N-methyl-4-piperidyl cyclobutylphenyl glycolate
Tox Number B006: 3-quinuclidinyl phenylcyclopentyl glycolate
Tox Number B007: Ditran
Tox Number B008: Benzetimide HCl
Tox number B009: L-2-α-tropinyl benzilate hydrochloride
Tox Number B010: L-2-α-tropinyl L-cyclopentylphenylglycolate
Tox Number B011: N-methyl-4-piperidyl cyclopentylmethyl-ethynyl glycollate (PCMG)
Tox Number B012: cis-2-methyl-3-quinuclidinyl cyclopentylphenyl-glycolate
Tox Number B013: 1-methyl-4-piperidyl phenyl-(3-methylbut-1-yn-3-enyl)-glycolate
Tox Number B014: 3-quinuclidinyl (1-hydroxycyclopentyl) phenylacetate
Tox Number B015: 3-quinuclidinyl cyclopentyl-(2 –propenyl)-glycolate
Tox Number B016: 4-(1-methyl-1,2,3,6-tetrahydropyridyl)-Methyl-Isopropyl-phenylglycolate
Tox Number B018: Benactyzine HCl (Amizil, Suvatil, Parasan, Nutinal)
Tox Number B022: atropine methyl nitrate (Eumydrin, AMN)
Tox Number B023: N-methyl-4-piperidyl isopropylphenyl-glycolate (EA 3834)
Tox Number B025: toxogonin-atropine-benactyzine (TAB)

Neither BZ nor any of the anticholinergic BZ-related compounds studied had any long-term sequelae associated with them. BZ and Benactyzine HCl produced short-term neurological and cognitive deficits in rats and mice respectively. Additionally, atropine methyl nitrate (AMN) administration seems to be related to immunomodulatory activity in rats, but it is unclear what physiological impact this may have – if any.

3-Quinuclidinyl benzilate (BZ, QNB)

No evidence was found for long-term sequelae associated with BZ exposure in humans or animals. However, animal testing with BZ has demonstrated short-term learning impairment after exposure.

An administration of BZ at the dose of 2.0 mg.kg-1 induced disorientation in rodents tested against various maze running activities and passive avoidance tests.[262,263,264] The behavioral alterations were found only when BZ was administered before training; well-trained rats showed no alteration in the test of spatial memory or avoidance. These results indicate that BZ impairs specifically the process of memory acquisition (learning), whereas retrieval of consolidated information (long-term memory) is not affected. Similar results on learning disruption have been found with scopolamine and other anticholinergics.[265,266,267]

Tox Number B002: N-Methyl-4-piperidyl cyclopentylphenyl glycolate

This compound is no longer in commercial use. No information on long-term sequelae associate to exposure was found.

Tox Number B003: N-methyl-4-piperidyl cyclobutylphenyl glycolate

There was no information available about long-term sequelae of exposure for this compound.

Tox Number B006: 3-quinuclidinyl phenylcyclopentyl glycolate

No information on long-term sequelae associated with exposure to this compound was found.

Tox Number B007: Ditran

The only recent publication discussing Ditran that could be found is on its historical use in toxic, antipersonnel projectiles (bullets, shells, etc.).[268] It is not currently in widespread clinical or commercial use today, and information on long-term effects of exposure to Ditran is absent from the medical, public health, and environmental science literature.

Tox Number B008: Benzetimide HCl

Benzetimide HCl is not in widespread clinical or commercial use today. There is no information on the potential long-term effects of exposure to this compound.

Tox number B009: L-2-α-tropinyl benzilate hydrochloride

L-2-α-tropinyl benzilate hydrochloride is no longer in widespread clinical or commercial use, and there is no recent scientific or medical information about its effects. There is no information on the potential long-term effects of exposure to this compound.

Tox Number B010: L-2-α-tropinyl L-cyclopentylphenylglycolate

Testing with this compound ended in the late 1960s. There is no information available on long-term effects of exposure to this drug.

Tox Number B011: N-methyl-4-piperidyl cyclopentylmethyl-ethynyl glycollate (PCMG)
There are no recent publications on PCMG, and there is no information on the potential long-term effects of exposure to this compound.

Tox Number B012: cis-2-methyl-3-quinuclidinyl cyclopentylphenyl-glycolate
No information was available about this compound in recent literature.

Tox Number B013: 1-methyl-4-piperidyl phenyl-(3-methylbut-1-yn-3-enyl)-glycolate
This anticholinergic is no longer in use today, and no information about long-term sequelae related to exposure was found.

Tox Number B014: 3-quinuclidinyl (1-hydroxycyclopentyl) phenylacetate
No recent information was available on this compound.

Tox Number B015: 3-quinuclidinyl cyclopentyl-(2 –propenyl)-glycolate
There is no recent information available on this compound.

Tox Number B016: 4-(1-methyl-1,2,3,6-tetrahydropyridyl)-Methyl-Isopropyl-phenylglycolate
There is no recent information on this compound.

Tox Number B018: Benactyzine HCl (Amizil, Suvatil, Parasan, Nutinal)
No information was found on long-term sequelae associated with the use of Benactyzine HCl.

There are, however, a few animal studies that suggests some short-term cognitive impairment may be brought about by the administration of benactyzine compounds, but that these side-effects will spontaneously resolve within a few weeks post exposure. Studies in mice have shown a decrease in the natural preference for novelty with administration along with decreased exploration and rearing. Other studies have suggested that benactyzine compounds decrease the ability of the animal to notice changes in its environment and to adapt its behavior accordingly.[269]

Tox Number B022: atropine methyl nitrate (Eumydrin, AMN)
There was no information available about long-term sequelae associated with AMN exposure. However, animal studies have demonstrated that atropine methyl nitrate increases FOS-like immunoreactivity selectively in the in the gut of rats. Specifically, this action takes place in the

mesenteric plexus, but not in the dorsal vagal complex or the dorsal motor nucleus of the vagus.[270] Still other studies have shown that atropine methyl nitrite does NOT suppress tumor necrosis factor release during endotoxemia, but another atropine compound, atropine sulfate does.[271,272,273] This is potentially important in mediating the response of pro-inflammatory cytokines to toxic insult or sepsis.

Tox Number B023: N-methyl-4-piperidyl isopropylphenyl-glycolate (EA 3834)

No recent studies were available on EA 3834 to analyze the potential long-term health effects of exposure.

Tox Number B025: toxogonin-atropine-benactyzine (TAB)

There is a substantial literature on TMB-4 and a less significant amount on TAB anticholinergic compounds. However, most of these studies examine the efficacy of TMB-4 and TAB and do not discuss long-term negative effects of exposure. In fact, a study of accidental overdose in more than 100 children with TMB-atropine autoinjectors found no negative sequelae resulting from intramuscular inoculation.[274]

2.4 LSD, Other Classical Hallucinogens & Lysergamides

Lysergic Acid Diethylamide (LSD), Psilocybin, DMT, and Mescaline

Psychedelics are not known to harm the brain or other body organs or to cause addiction or compulsive use.[275,276] LSD and psilocybin mushrooms are also consistently ranked by drug-abuse experts as much less harmful to the individual user or to society than alcohol.[277,278,279,280]

No Long-Term Sequelae

A number of recent studies have found no long-term negative effects of LSD or other classical hallucinogen (psilocybin, DMT, & mescaline) exposure. The conclusions of these studies are different from earlier individual case reports of flashbacks and other cognitive disorders associated with LSD use, because they look at a large number of cases from a population survey, or amass a large amount of data by following a population across a significant amount of time.

For example, Krebs and Johansen examined the prevalence of mental-health problems in U.S. hallucinogenic drug users by pooling data from the National Survey on Drug Use and Health (NSDUH), years 2001-2004, yielding 130,152 respondents.[281] After the data were culled for age and demographic characteristics to make them representative of the U.S. population, the researchers were left with 21,967 samples. 17486 individuals (80.1%) reported use of LSD. Symptoms indicators for eight DSM-IV psychiatric disorders were used, and included: panic disorder, major depressive episode, mania, social phobia, general anxiety disorder, agoraphobia, post-traumatic stress disorder, and non-affective psychosis. These researchers found no significant associations between lifetime use of any psychedelics, lifetime use of specific psychedelics (LSD, psilocybin, mescaline, peyote), or past year use of LSD and increased rate of any of the mental health outcomes. Rather, in several cases psychedelic use was associated with lower rate of mental health problems.[280] Krebs and Johansen suggest that psychological disturbances or severe flashbacks previously associated with LSD use actually arise from other concurrent psychiatric problems, and not from the drug-use itself.[280]

Another study utilizing the NSDUH from 2008 – 2011, pooled data from 19,299 psychedelic drug users affirmed the findings reported above.[282] Additionally, the study found no association between LSD or psilocybin use and suicidal thoughts, plans, or attempts. Rather, among people with childhood depression, those who had used psychedelics had lower likelihood of past year suicidal thoughts and plans.

A study from a group of researchers at the University of Alabama, Birmingham also utilizing the NSDUH (2008-2012) found similar low prevalence of hallucinogen use and psychological distress, and suicide thoughts, plans, or attempts.[283] This work found that classic psychedelic use was associated with a significantly reduced odds of past month psychological distress [weighted odds ratio (OR)=0.81 (0.72–0.91)], past year suicidal thinking [weighted OR=0.86 (0.78–0.94)], past year suicidal planning [weighted OR=0.71 (0.54–0.94)], and past year suicide attempt [weighted OR=0.64 (0.46–0.89)], whereas lifetime illicit use of other drugs was largely associated with an increased likelihood of these outcomes.[282]

Another publication reporting on long-term LSD self-experimentation amongst a small group (n=22) of mental health professionals found no long-term negative effects from the drug use.[284] Also, all but two of the counselors recorded enrichment in the sphere of self-awareness.

Hallucinogen Persisting Perception Disorder

Prior to the use of data from the large population studies reported above, the use of LSD or related substances was thought to cause flashbacks in some people. However, there is no strong correlation between the number of times a person has taken the drug and the likelihood that they develop hallucinogen persisting perception disorder, so the condition may result following a single LSD experience or never appear despite hundreds of LSD experiences.[285] Hermle states that in light of recent clinical evaluations that previous estimates of HPPD prevalence (5% - 54%) were vastly overestimated and that these visual disturbances occur in less than 5 percent of psychedelic drug users.[286]

Nevertheless, the clinical literature of the past decade describes a defined flashback syndrome called hallucinogen persisting perception disorder (HPPD). The four visual illusions most described as part of HPPD are: macropsia (objects are perceived larger than their actual size), micropsia (objects are perceived smaller than their actual size), pelopsia (objects are perceived nearer than they actually are, and teleopsia (objects are perceived much further away than they actually are).[287] Some researchers studying flashbacks have divided HPPD divide it into two types:

- **HPPD 1:** A generally short-term, non-distressing, benign and reversible state accompanied by a pleasant affect.[287]
- **HPPD 2:** A generally long-term, distressing, pervasive, either slowly reversible or irreversible, non-benign state accompanied by an unpleasant affect.[288]

Both types of HPPD can contain the same visual imagery as experienced on the drug, or on occasion, new imagery presented in a hallucinogenic manner.[289] Lerner and colleagues have suggested that the principal difference between these two conditions rests on the patient's perception of impairment and disability.[288] They have also noted that HPPD I and II onsets may be preceded by already preexisting mental disorders such as anxiety, mood, somatoform, sleep and dissociative disorders or severe mental illnesses like schizophrenia, but may also contribute to the development of these disorders acting as a trigger.[288] Additionally, Litjens reviewed clinical HPPD cases and found that the majority of cases were attributed to drugs with agonistic effects on serotonergic 5-HT_{2A} receptors like LSD, but also like ecstasy (MDMA), which is not generally considered a hallucinogen.[290] He also proposes that serotonergic neurotransmission and the 5-HT_{2A} receptor, which are involved in low-level visual processing, and as such are possible targets for both classical hallucinogens and MDMA visual changes, such as HPPD.[289]

Rhabdomyolysis-Related Complications

There are a small number of human case reports on LSD-related rhabdomyolysis, which is a syndrome resulting from skeletal muscle cell injury and the subsequent release of intracellular contents into the circulation.[292] Presenting symptoms and signs include myalgia, limb weakness, and electrolyte abnormalities. Although technically not necessary for diagnosis, myoglobinuria and elevated creatine kinase (CK) are important markers of muscle injury.[291,292] Although rhabdomyolysis is usually reversible, it requires long-term follow-up treatment.[293]

LSD (free base), LSD (tartrate salt), LSD (maleate salt)

No information on long-term sequelae were found on LSD in its unstable free-base form, or in its tartrate or maleate salt forms.

Acetyl lysergic acid diethylamide (ALD)

There was no recent information about long-term negative health effects of ALD.

Bromo-lysergic acid diethylamide (BOL)

There was no recent information about long-term negative health effects of BOL

2.5 Oximes, Irritants, & Incapacitants

Table 10. Oximes, Irritants and incapacitants with No Evidence for Long-Term Sequelae
Oxime
Toxogonin, Obidoxime chloride
Trimedoxime (TMB4)
Pralidoxime methane sulfonate
Irritant
(CA) Bromobenzyl cyanide
(CN) Chloroacetophenone (Mace™)
(DM) Adamsite
Capsicum (Pepper Spray)
EA 1778 (nonanoyl morpholide), MPK
EA 2097, Benzylidene malonitrile
(CR), EA 3547, Dibenzoxazepine
(CHT), EA 4923, 1-Methoxy-1,2,5-cycloheptatriene
Incapacitants
EA 2148-A, Phencyclidine (PCP)
218437, an indolylalkyl piperazine (Oxypertine)
219362
220548, Benzomorphan
302034, Benzomorphan butyrophenone
EA 1476, EA 2233, EA 2233 2-8, Dimethylheptyl pyran (DHMP)

Oximes

Toxogonin, Obidoxime chloride

Despite many publications on the acute adverse effects of oximes, there is no discussion of the long-term negative health impact of use in the recent literature (7/2006 – 12/2015). Historical work by Balali-Mood found that obidoxime was hepatotoxic at high recommended doses of 8 mg/kg initially and 3 mg/kg/hr.[294] A more recent reference by Balali-Mood confirmed these early results and call for the need to monitor liver function during obidoxime treatment.[295] Unmonitored and untreated, this hepatotoxicity can lead to jaundice or hepatitis, but not all studies have found this to be true.[296] Other adverse clinical effects of oximes include hypotension, cardiac arrhythmia (including cardiac arrest after rapid administration), headache, blurred vision, dizziness and gastric discomfort.[295]

Oxidative Stress

Work done by Drtinova and Pohanka in guinea pigs has shown that the level of low molecular weight antioxidants decreased in all the organs (except kidneys) after administration of obidoxime.[296] This work was done by intramuscularly injecting groups of 3-month old guinea pigs with a five percent LD_{50} dose of obidoxime (4.15 mg/kg).[297] The frontal lobe, cerebellum, spleen, liver, and kidney were collected after euthanasia at 15, 30, 60, 120, and 240 minutes post-exposure and assessed for antioxidant markers using the ferric reducing antioxidant power assay (FRAP), thiobarbituric acid reactive substances assay (TBARS), glutathione S-transferase (GST) assay, and glutathione reductase (GR) assay.[296]

Obidoxime caused a decrease of FRAP ($p = 0.01$) in the frontal lobe after 15 minutes and in the spleen after 60 minutes ($p = 0.05$). TBARS levels were also significantly reduced in the frontal lobes and cerebellum at 15 minutes' post exposure and beyond ($p = 0.01$). Furthermore, GR was significantly increased ($p = 0.01$) in the liver after 15 minutes when compared to controls.[296]

It is unclear how disruptions in antioxidant homeostasis and subsequent oxidative stress caused by obidoxime exposure is related to specific pathogenesis and toxicity, but clinical studies have shown that antioxidants are often depleted in the brains of patients who suffer from neurodegenerative disease.[298,299]

Oxidative stress has also been implicated as a factor in the development of some cardiovascular diseases such as myocardial infarction and atherosclerosis.[300] Historical studies also implicate oxidative stress in chronic fatigue syndrome.[301] That said, oximes are generally cleared from the body soon after exposure, and there is currently no clear evidence linking the oxidative stress caused by obidoxime administration and disease in humans. Repeated administration of

obidoxime across several days or a week, however, may cause tissue damage in multiple organs which, if severe enough, may predispose patients to other illnesses.

Trimedoxime (TMB4)

A recent examination of symptoms produced by accidental injection with atropine and TMB4 autoinjectors in Israel, found no adverse reactions related to TMB4 exposure in adults.[302] This study was based on data collected from the Israel Poison Information Center, and the Assaf Harofeh Medical Center over a two-year period. The absence of adverse effects in the study subjects was likely related to the relatively low dose of TMB4 in the autoinjectors (80 mg). Earlier studies (before 7/2006) sometimes reported more severe adverse effects of TMB4 use, but these were usually observed after larger doses (187 – 262 mg) of the oxime.

Pralidoxime methane sulfonate

The literature search found no recent publications (from 7/2006 – present) which clearly link pralidoxime exposure to long-term adverse health effects. The only recent publications found discussed the acute toxicity and adverse short-term effects of exposure.

Despite the beneficial effects of pralidoxime first noted with parathion poisoning, its effectiveness has been much debated. Historical trials in the developing world, where organophosphate (OP) poisoning is an important public health problem, noted that low-dose infusions of pralidoxime may actually increase morbidity and mortality in patients.[303, 304, 305] A recent meta-analysis by Buckley and Eddleston, however, suggested that these clinical trials used suboptimum doses and inadequate delivery regimes of pralidoxime, that investigators did not achieve the plasma concentrations of oxime recommended by the World Health Organization, and that these design issues were the cause of their poor outcomes.[306]

A more recent clinical trial by Pawar examining the efficacy of high-dose pralidoxime for OP poisoning found the administration of the oxime improved morbidity and treatment outcomes.[307] In that trial, patients were given a dose of oxime upon admission and were then randomly assigned to control and study groups (100 patients per group.) Controls were given a bolus dose of 1g pralidoxime per hour every 4 hours for 48 hours. The study group had a constant infusion of 1g per hour every hour for 48 hours. Patients receiving the high-dose pralidoxime regimen required less atropine during the first 24 hours than controls [median 6 mg vs 30 mg; difference 24 mg (95% CI 24-26, $p < 0.0001$)]. Eighty-eight percent of controls and 64 percent of high-dose patients needed intubation during admission to hospital (relative risk (RR) = 0.72, 0.62-0.86, $p = 0.0001$). Control patients required ventilatory support for longer [median 10 days vs 5 days; difference 5 days (5-6, $p < 0.0001$)].[306]

Irritants

(CA) Bromobenzyl cyanide

There were no publications available from 7/2006 to 12/2015 that discussed adverse effects or long-term sequelae of exposure to CA.

(CN) Chloroacetophenone (Mace™)

Older animal studies (rat, rabbit, guinea pig and mouse) from the 1970s examining the inhalational pathophysiology and pathogenesis of CN at LD_{50} exposures found that animals surviving intentionally high initial doses sustained only acute injury, not long-term serious damage.[308] Historical reports also describe several human deaths associated with aerosol exposure, but these exposures took place in enclosed spaces and over long periods of time, so the inhaled dose of CN was quite high.[309,310,311] Serious acute injuries, including respiratory distress, chemical pneumonitis, pulmonary edema, and hepatocellular injury have also been reported in historical and in recent literature, as have non-serious cases of allergic dermatitis.[312,313,314] Despite the large number of papers (most published before 7/2006) on the acute effects of CN, the literature search did not find any information about long-term negative health effects of exposure.

(DM) Adamsite

Adamsite and other arsenicals are not commonly used anymore because of the moderately high toxicity in humans.[315] No information was found on the long-term sequelae of Adamsite exposure published between the periods of 7/2006 – 12/2015.

Capsicum (Pepper Spray)

Although there is no systematic review of long-term negative sequelae associated with pepper-spray attacks, there are a few case reports of ocular and respiratory injuries sustained during the course of pepper-spray attacks lasting for months post exposure.[316,317] Ocular injuries include corneal erosions, abrasions, and ulcers, respiratory problems include pulmonary edema and bronchospasm, and even death.[318,319,320] An examination by Toprak and colleagues of 10 deaths in which riot-control agents were either the principal or contributory cause of death, showed that 7 of the lethal cases were associated solely with a pepper spray product.[321]

Most of the serious complications, however, resulted from exposure to very high doses,[322] or from the subject being very close to the spray, smoke, or exploding canister.[315] Pre-existing health conditions, such as asthma, COPD, or cardiovascular disease; or interaction with prescribed medications or illegal drugs may also influence the development of severe injuries.[323,324]

Serious injuries resulting from exposure to capsicum have been estimated to range between 2.7% and 15% of exposures, depending upon the setting.[325]

EA 1778 (nonanoyl morpholide), MPK

Despite its recent use in Russia,[326] the literature search found no information in English on the long-term health effects of EA 1778 published between 7/2006 and the present.

EA 2097, Benzylidene malonitrile

Benzylidene malonitrile is the parent compound of the CS agents (-chlorobenzylidene malononitrile). The literature search found no information on the long-term health effects of EA2097.

(CR), EA 3547, Dibenzoxazepine

The literature search uncovered no recent work on long-term negative health effects from CR exposure in animals or humans.

(CHT), EA 4923, 1-Methoxy-1,2,5-cycloheptatriene

The literature search uncovered no recent (7/2006 – 2015) publications on the long-term health effects of CHT.

Incapacitants

EA 2148-A, Phencyclidine (PCP)

Despite there being numerous papers on the use of PCP exposure to model schizophrenia in rodents, the literature search failed to uncover information about potential long-term sequelae resulting from PCP exposure. One of the reasons for this is that many of the animal studies purported to study, "long-term," changes in behavior[327,328] or brain receptors[329,330] resulting from PCP exposure, but only measured behaviors for 2-to-3 weeks after drug dosing had ceased. Other studies called the difference between adolescence and adulthood slightly more than 1 month (50 days postnatal as opposed to 90 days or older.)

In regards to the long-term effects on humans, older publications tend to emphasize how phencyclidine *causes* psychosis, schizophrenia, or other psychological disturbances,[331] whereas more recent papers tend to discuss how PCP use, "unmasks," or "uncovers" innate problems.[332] Therefore it is impossible to confidently assign PCP exposure as the cause of these disorders or to mark the disorders as sequelae.

218437, an indolylalkyl piperazine (Oxypertine)

This literature search was unable to uncover recent publications (7/2006 – present) on potential long-term sequelae related to oxypertine exposure. This is probably because it is more common for clinicians today to prescribe a second-generation antipsychotic with greater efficacy and safety profile, than a first-generation drug like oxypertine. The compound is also not discussed in the National Academy of Sciences summaries on the human-exposure trials.

219362

No information, historical or recent, was found on this compound, and it is also not discussed in the National Academy of Sciences summaries on the human-exposure trials.

220548, Benzomorphan

Descriptions of potential sequelae found in the historical and recent literature for pentazocine almost all deal with long-term use or abuse of the drug, and not a single or a handful of exposures as was experienced by volunteers in the trials run by the U.S. military and intelligence community.

The most commonly described sequelae is cutaneous scarring from injection.[333, 334] Patients (chronic users) can present with deep skin ulcers and sinuses over accessible sites, and the cutaneous sequelae include hyperpigmented halos around injection ulcers. These ulcers heal with central hypopigmentation, along with skin fibrosis, chronic panniculitis, edema, woody induration, phlebitis, cellulitis, and symmetrical myopathy. On occasion, injection-site necrosis and sepsis have also occurred, and thus sometimes required amputation. Fibrous myopathy is a rare but conspicuous complication of prolonged pentazocine injection, with subsequent limb contractures.[335]

Additionally, the potential for long-term sequelae related to morphine use (addiction, respiratory depression or failure, appetite suppression and weight loss, nausea and vomiting, and negative psychosocial behaviors) were also examined as part of the literature review. Once again, all of the potential long-term sequelae were related to long-term use of morphine and/or escalating doses of the drug.

Benzomorphan exposure is not discussed in the National Academy of Sciences summaries on the human-exposure trials.

302034, Benzomorphan butyrophenone

No information, historical or recent, was found on long-term sequelae associated with this compound. The compound is also not discussed in the National Academy of Sciences summaries on the human-exposure trials.

EA 1476, EA 2233, EA 2233 2-8, Dimethylheptyl pyran (DHMP)

Although cannabinoid use has been linked with specific changes in immune function, including 1.) An alteration in cytokine production and secretion (suppression of pro-inflammatory cytokines) in most immune system cell lines, including central nervous system cells[336] and, 2.) A general change in the immune response from Th1 (cell-mediated) to Th2 (humoral mediated),[337] it is unclear what the functional impact of these changes may be – if any.

Additionally, some historical population research has shown that cannabinoid users have a two-fold higher risk of developing schizophrenia than matched non-users.[338] And that elimination of cannabinoid use would reduce the incidence of schizophrenia by approximately 8 percent,[339] these studies are flawed and do not differentiate between pre-existing conditions and those that may be, "caused," by DMHP use.

Lastly, most of the studies looking at the potential links between DMHP and neuropsychiatric conditions studied it in repeat and often heavy users of cannabinoid drugs. The volunteers exposed to one or only a few exposures in human trials may not have experienced the same biological processes described in the studies cited.

2.6 Miscellaneous Traditional Chemical Warfare Agents

Table 11. Traditional Chemical Warfare Agents with No Evidence for Long-Term Sequelae
Lewisite
Cyanide, Hydrogen cyanide (HCN), AC
Phosgene Oxime (CX)

Lewisite

Despite the severe acute effects of lewisite, no information on long-term symptoms or sequelae related to exposure exists. One can surmise, however that mid-to-long term incapacitation may occur from skin and eye burns, pulmonary injury, and systemic illness. The eye lesions produced by lewisite are particularly serious: blindness will follow contamination of the eye with liquid lewisite unless decontamination is prompt.[340]

Cyanide, Hydrogen cyanide (HCN), AC

Although the scientific literature is full of studies describing the acute effects of cyanide exposure, most of these publications are limited to the description and mitigation of acute symptoms. Only a few case reports from any time period attempt follow-of discharged patients and discuss the long-term sequelae experienced by some survivors of cyanide exposure. Because neurological sequelae as a consequence of HCN exposure occurs in only one case report published between 7/2006 – 12/2015, it is discussed below.

Neurological impairments are the most frequently described long-term negative effects. A recent case report from Australia discusses the neurological deficits in a woman who attempted suicide by ingesting cyanide salts. Several days after admission and after the resolution of her acute physical symptoms, a psychiatric assessment showed marked impairment in episodic memory, particularly for day-to-day events. Neurological assessment was unremarkable and she displayed none of the symptoms: Parkinsonism, dystonia, or dyskinesia sometimes described in survivors of cyanide exposure.[341] MRI-scan of the brain at 1-week post-injury showed extensive long repetition time (TR) high signal and restricted diffusion in the hippocampus and globus pallidus bilaterally. These changes from normal architecture were considered consistent with anoxic brain injury. Memory deficits, visual recall difficulties and mild problems concentrating and dividing attention continued after transfer to a mental health facility three weeks after admission.

A repeat assessment five months later showed a general improvement in intellectual ability and in registration of verbally presented material (which were then assessed at a low-average level). Her ability to learn new verbal information, as well as her visual recall had also improved in the later assessment, although they remained at an impaired level. A second MRI-scan showed decreased high signal in the hippocampi, suggestive of resolution of acute edema noted in the first scan. In the follow-up MRI, the hippocampi were also noted to appear more atrophic.[340]

Although cyanide exposure is associated with severe acute cardiovascular symptoms, such as ventricular fibrillation, cardiac arrest, cardiac rhythm and repolarization disorders, and intracardiac conduction disorders, these problems either lead to the death of the patient, or apparently resolve before discharge.[342] No reports on long-term cardiac sequelae following cyanide exposure were found.

Phosgene Oxime (CX)

Despite severe acute effects, there is no specific information available about the long-term sequelae that may arise as a consequence of exposure to CX.

If an individual survives an offensive attack with phosgene oxime, the long-term negative effects may be *hypothesized* based on the acute effects. Keratitis and pigment problems may follow mild-to-moderate dermal exposure, with the potential for peripheral neurological sequelae seen in cases of high-dose exposure.

Mild-to-moderate inhalation exposure may produce respiratory disability that will resolve in weeks to months, with higher-dose exposures producing permanent respiratory disability such as shortness of breath, wheezing, easy fatigability, and a possible predisposition to lung diseases such as bronchitis and COPD, etc. Ocular exposures will likely lead corneal scarring that may or may not resolve over time. High-dose exposures to the eyes will almost certainly lead to vision problems or permanent blindness. Since there is no treatment for the symptoms of phosgene oxime, the amount and quality of supportive therapy, pre-existing health status of the patient, and potential relevant genetic polymorphisms may influence the development of long-term negative symptoms following exposure.

2.7 Environmental Pollutants and Toxic Compounds

Table 12. Environmental Pollutants with No Evidence for Long-Term Sequelae
Nitrogen dioxide
Propylene glycol

Nitrogen dioxide

In recent years there have been a number of studies linking NO_2 exposure to a wide variety of serious illnesses including cardiovascular and respiratory diseases, diabetes, and some cancers. However, most of these studies are based on long-term (sometimes lifetime) exposures, and so they are not relevant to the potential development of sequelae experienced by soldiers in the short-term human exposure trials conducted by the military in the 1950s through the 1970s. There are, however, a number of *short-term exposure* studies that have found increases in mortality from a variety of causes linked to short-term increases in nitrogen dioxide in the air. Although none of these studies discuss the potential for long-term sequelae *per se*, a summary of the most notable studies follows.

As part of the China Air Pollution and Health Effects Study (CAPES) study, Chen and colleagues found that small increases in NO_2 levels were associated with increased mortality in 17 Chinese cities.[343] In the combined analysis, a 10-$\mu g/m^3$ increase in two-day moving averaged NO_2 was associated with a 1.63% increase [95% posterior interval (PI), 1.09 to 2.17] in total mortality, a 1.80% increase (95% PI, 1.00 to 2.59) in cardiovascular mortality, and a 2.52% increase (95% PI, 1.44 to 3.59) increase in respiratory-related mortality.[342] These associations remained significant after adjustment for ambient particles or sulfur dioxide (SO_2), indicating the specific role of NO_2 in increased mortality. Mortality also varied with age (higher in older individuals), sex (higher in females), and educational attainment (higher in those of lower socioeconomic backgrounds), but these relationships were not statistically significant.[342] These results are similar to those found in the Air Pollution on Health: a European Approach (APHEA)-2 project which examined the relationship between NO_2 levels and total, cardiovascular and respiratory mortality in 30 European cities.[344] The Public Health and Air Pollution in Asia (PAPA) study also found an excess total mortality of 1.19%, for each 10 $\mu g/m^3$ increase in NO_2 in three Chinese cities (Hong Kong, Shanghai, and Wuhan).[345]

A recent meta-analysis of mortality and air pollution (NO_2 levels) in 17 Chinese cities found an excess risk for total mortality of 1.30% (95% CI: 1.19, 1.41) for each 10 µg/m3 increase in NO_2. Cardiovascular mortality was increased by 1.46% (95% CI: 1.27, 1.64), and respiratory mortality

increased by 1.62% (95% CI: 1.32, 1.92) with similar short-term increases in NO_2.[346] Another recent meta-analysis of air pollution levels and cardiovascular disease mortality found a 1.30% (95% CI: 0.45, 2.14) increase in coronary heart disease deaths in 8 Chinese cities with a 10 $\mu g/m^3$ increase in NO_2 levels.[347]

Although all of the short-term exposure studies described above use mortality as an endpoint, there is a small but significant relationship between increased mortality and increases in air pollution (NO_2) in a wide-variety of geographic settings. Although specific data on the role of NO_2 in the potential development of long-term sequelae are lacking at this time there seems to be an exacerbation of existing (even if undiagnosed) conditions by short-term increases in outdoor air pollution.

Propylene glycol

Acute propylene glycol toxicity sometimes occurs in hospital situations with continued intravenous infusion of medications and some antibiotics, because of the presence of PPGs in the intravenous solution.[348] Although this toxicity can have serious symptoms (significant hypotension, lactic acidosis, and decreased renal function), symptoms resolve when infusion is stopped, and exposure produces no long-term sequelae.[349]

Recent reviews and meta-analyses of the toxic effect of propylene glycols in electronic cigarettes is inconclusive about how harmful inhaled PPGs are.[350,351] Some studies report negative respiratory effects, such as mouth and throat irritation and the development of a dry cough, and other studies do not. To some degree, this variability of data is caused by methodological problems in the studies, including a lack of long-term follow-up of subjects. Additionally, some studies are sponsored by e-cigarette manufacturers.[352]

Kienhuis and colleagues recently found that one puff (50-70 mL) of a "shisha-pen" e-cigarette results in an exposure to propylene glycol of 430 to 603 mg/m^3. This single puff produces exposure concentrations higher than the points of departure for human airway irritation, which have been estimated to be 309 mg/m^3.[353] Additionally, most e-cigarette studies do not examine the health effects of the products with prolonged use. This is a significant gap because a historical animal study showed that repeated exposure (6 h per day; 5 days per week) for 90 days at 1,000 and 2,200 mg/m^3 caused *irreversible* respiratory damage.[354]

Historical research generally concludes that the propylene glycols are not genotoxic or carcinogenic, and they do not cause developmental abnormalities or sensitization.[355] A recent study from Sweden by Choi and colleagues, however, found higher indoor levels of propylene glycols are associated with a 1.5-fold greater likelihood of asthma (95% CI, 1.0 – 2.3), 2.8-fold greater

likelihood of rhinitis (95% CI, 1.6 – 4.7), and 1.6-fold greater likelihood of eczema (95% CI, 1.1 – 2.3) in children.[354] These increased risks for disease remain after adjustment for a wide variety of other factors which include but are not limited to gender, secondhand smoke, parental allergies, and wet cleaning with chemical agents. These researchers propose a novel hypothesis that propylene glycols in indoor air exacerbate or induce the multiple allergic symptoms such as asthma, rhinitis, and eczema, as well as IgE sensitization.[356]

2.8 Barbiturates, Stimulants, & Antidepressants

Table 13. Barbiturates, Stimulants and Antidepressants with No Evidence for Long-Term Sequelae
Amobarbital
Phenobarbital
MDMA
Iproniazid

Amobarbital

Amobarbital is generally regarded as safe. A small number of case reports were found that discuss seizure or stroke during intracarotid amobarbital dosing,[357,358] but analysis of these publications suggest that these events are procedure-related and not substance-related.

There were some papers on the negative neurobehavioral effects on children born to women who used or abused the drug during pregnancy, but these were not thought to be relevant to the demographics of the volunteers in the historical military-sponsored human trials.

Phenobarbital

Studies have implicated phenobarbital in the development of a number of adverse reactions, some of which were acute and transient like cutaneous reactions[359] and eosinophilia with systemic symptoms (DRESS).[360] Although these events can sometimes be severe, symptoms generally resolve when medication is stopped, and they are not associated with long-term sequelae.

A national-level study in Taiwan also implicated several anti-epileptic drugs with acute hypothyroidism.[360] Using the Taiwan National Health Insurance Research Database (NHIRD) from 2004 to 2010, Lai and colleagues found that the adjusted sequence ratio of thyroxine use after any anti-epileptic drug was 1.75 (99% C: 1.58–1.94), and 1.21 (99% CI: 1.08–1.34) for phenobarbital.[361] Despite the serious effects of hypothyroidism, these adverse events were acute and not chronic or long term.

Phenobarbital use has also been linked with other adverse events with more serious and long-term consequences, such as the development of liver cancer.[362] This relationship is particularly strong in some historical studies. A long-term Danish cohort study found a more than three-fold excess risk of any liver cancer in patients who took phenobarbital.[363] This study by Olsen and colleagues found relative risks (RRs) of 4.7 [95% confidence interval (CI) 3.2–6.8] of liver

cancer and 2.2 (95% CI 1.2–3.5) of biliary tract cancers. More recent studies, however, have concluded that such apparently-high excess risks could be largely or completely attributed to the use of thorotrast, a contrast medium used in the past in epileptic patients for cerebral angiography.[364] Thorotrast is a known hepatic carcinogen, and when the thorotrast-treated cases were removed from the Danish sample, the association between phenobarbital and liver cancer was no longer significant.

Additionally, the U.S. Food and Drug Administration released a review in 2008 that reported a 2-fold increased risk of suicidal ideation or behavior for 11 anti-epileptic drugs that include phenobarbital (odds ratio, OR, 1.80, 95% confidence interval, CI, 1.24–2.66).[365] This study has been criticized as methodologically unsound (i.e., it grouped anti-epileptic medications with very different mechanisms of action and associated relative risks) by a number of authors,[366,367] and no association between suicide and phenobarbital is recognized today.

A major meta-analysis by Zhang and colleagues performed using the Cochrane Central Register of randomized controlled trials (1800-2009), Medline (1966-2009), Embase (1966-2009), and three Chinese databases found that the data did not demonstrate any evidence of association between phenobarbital and a higher risk of adverse events.[368] However, they did find that phenobarbital appeared to be associated with a higher rate of adverse drug reaction related withdrawal (ADR-related withdraw), when compared to carbamazepine, valproic acid and phenytoin.

MDMA

Animal studies have demonstrated that MDMA use produces long-term changes in the brain's serotonergic system. A study by Kirilly and colleagues using rats showed that a *single* MDMA exposure produced significant (20–40%), widespread reductions in serotonin transporter (5-HTT)-IR fiber density in most investigated brain areas at 7 and 21 days. This occurred in all regions of the cerebral cortex, and hippocampus, several nuclei of the hypothalamus, and some cell groups of the brainstem. Recovery of serotonergic neuronal density to normal by the end of the 180-day observation period was seen in most brain areas except the hippocampus.[369] In addition to neuronal damage, significant decreases in REM latency were found in the rats at 7 (-55%) and 21 (-53%) days after MDMA administration.

Interestingly, *pretreatment* with MDMA three weeks *prior* to the experiment produced significant long term decreases in 5-HTT-IR fiber density in brain areas involved in the regulation of aggression 21 days after MDMA administration. The animals showed a significant increase in kicking (H=18.912, p=0.010) and a small decrease in grooming ((H=24.473, p=0.008) and social behavior (H=24.340, p=0.006). [368]

Although, many of the alterations in the serotonergic system observed by Kirilly returned to normal by the end of the observation period, it is important to note that the rats received only *a single dose* of MDMA. With multiple or habitual dosing, changes may persist of longer periods of time, or may be permanent.[368]

Brain neuroimaging studies have suggested that *human* MDMA users may also have long-lasting changes in brain function consistent with decreased serotonin transporter density.[370] Additionally, a study by Reneman investigated the effects of moderate and heavy MDMA use on several aspects of cognitive function. These researchers found that heavy and ex-MDMA users performed significantly poorer on memory function tasks than controls, but that moderate users had no memory deficits.[371] Neither the heavy nor the moderate user groups differed in performance on reaction time tests or on measures of attention and executive function relative to controls. The results of this study suggest that sporadic or moderate MDMA use produces no long-term sequelae.

Iproniazid

Iproniazid was an MAO-inhibitor drug that was first labelled as an antidepressant in 1958, but was removed from major portions of the world market in 1961 because of its ability to induce hepatocellular injury and chronic hepatitis. Because it is rarely used today as an antidepressant, all of the publications found that discuss its association with liver injury were published before July 2006 – the early cutoff date for information in this report. Even the recent reviews of that explore the association between medications and liver problems;[372] only cite iproniazid-related papers from the 1970s and early 1980s.

2.9 Miscellaneous Drugs and Diagnostic Substances

Table 14. Miscellaneous Drugs and Diagnostic Substances with No Evidence for Long-Term Sequelae
Phenazone
Indocyanine green
Aminohippuric acid (PAH)
Bromsulphthalein (BSP)

Phenazone

Phenazone is a non-steroidal anti-inflammatory drug used as an analgesic and antipyretic. It is a commonly used drug and generally regarded as safe. None of the databases consulted had recent publications linking it to toxicity, adverse effects, or sequelae.

Indocyanine green

Indocyanine green (ICG) is a cyanine dye used in medical diagnostics. It is also commonly used to improve the visualization of preretinal tissues during repair of macular holes or chromovitrectomy. The most common long-term sequelae resulting from the use of indocyanine green is found in ophthalmological surgery; ICG has been found to be toxic to the retinal pigment epithelium (RPE). Surgical observation has suggested that the toxic effect of ICG on the retina is dose-dependent.[373] Indeed, a comparative test of the effect of ICG and other contrast dyes on retinal cell lines at five different concentrations (1, 0.5, 0.25, 0.05, and 0.005 mg/mL) found that ICG significantly reduced cell viability after 3 minutes of exposure at all concentrations ($p<0.01$). Additionally, the expression of pro-apoptotic *Bax, cytochrome-c* and *caspase-9* were upregulated at the mRNA and protein level after ICG exposure.[374]

ICG-related damage to the retina has long been thought to result in lower visual acuity than expected after surgery.[375,376] For example, a study from Korea showed that indocyanine green-related RPE atrophy in an elderly woman resulted in best-corrected visual acuity of 20/63 in the right eye and 20/125 in the left eye. However, a recent meta-analysis from China suggest that ICG only slows the *rate* of vision recovery, and that visual acuity between the ICG treated group and the non-ICG treated group is only lower for the first year after surgery.[377]

Aminohippuric acid (PAH)

Aminohippuric acid (PAH) is generally regarded as safe. None of the databases consulted had any recent publications on potential toxicity, adverse effects, or sequelae.

Bromsulphthalein (BSP)

Bromsulphthalein (BSP) is generally regarded as safe. BSP is a commonly used contrast dye that is safe. None of the databases consulted had any recent publications on potential toxicity, adverse effects, or sequelae.

2.10 Miscellaneous Other Compounds

Table 15. Miscellaneous Other Compounds with No Evidence for Long-Term Sequelae
12202
Pyridine
CS Arsenic
5-HTP
Octylamine
Chloropicrin

12202

No references could be found for this compound. Even after many searches like 12202 AND Chemical Warfare OR Edgewood. If further information can be provided, references will be identified and evaluated during the revision phase of the project.

Pyridine

Most references on pyridines that have been published after 7/1/2006 have to do with pyridine compounds as treatments for a wide-variety of illnesses from allergies to cancer. There is also a robust literature on biomarkers and detection. The important work on toxicology, adverse effects and sequelae is very old and beyond the range of this report.

CS Arsenic

No recent information could be found in any open-source database on the CS-Arsenic compound.

5-HTP

The most common adverse effects of 5-HTP include nausea, vomiting, and diarrhea. These effects are probably due to the conversion of 5-HTP to serotonin in the periphery, and subsequent increases in gut motility.[378] Less commonly, headache, insomnia, and palpitations can occur. Gastrointestinal effects are usually moderate and often lessen or disappear once a steady dosage is achieved. Intravenous administration of 200 to 300 mg of 5-HTP can induce confusion, memory impairment, and symptoms of behavioral activation (primarily anxiety). However, none of these effects is long-term and generally resolve when dosing stops.

It is worth noting that over-the-counter sales of the 5-HTP precursor amino acid L-tryptophan caused an epidemic of eosinophilia myalgia syndrome (EMS) that affected over 1,500 people

and caused at least 38 deaths in 1989-1990.[379] The cause of this outbreak was found to be contaminants in the L-tryptophan that were traced to a single manufacturer in Japan. The FDA subsequently banned the sale of over-the-counter L-tryptophan, and a swift resolution of the EMS epidemic followed.

Since the introduction of 5-HTP onto the nutritional supplement market, a handful of cases of EMS-like illness have been reported in people taking the supplement.[380] These cases sparked fears that 5-HTP might also cause EMS. However, none of the cases has been definitively linked to 5-HTP, despite 20 years of use.[381]

Octylamine

No recent references were found for the potential long-term negative health effects of octylamine in any of the databases searched.

Chloropicrin

A 2009 review of accidental agricultural exposures that took place in California between 1992 and 2003 found many reports of acute illness among people exposed to chloropicrin, but no long-term sequelae resulting from acute exposures.[382] The 28 incidents reviewed in this paper resulted in 318 reports of illness associated from off-site or drift chloropicrin exposure. The most common complaints of those exposed were eye irritation (280 cases; 88.1%), respiratory irritation (173 cases; 54.4%), and systemic illness such as headache or nausea (149 cases; 46.9%).[381] Skin irritation was reported by only five people (1.6%). All of the symptoms experienced by the people exposed to chloropicrin in these events resolved, and there were no reported long-term effects or sequelae.[381] Similar acute symptoms were experienced by people exposed to chloropicrin in 2005 in Salinas, California, with no resulting long-term illnesses.[383]

3.0 Military Exposures and Health Outcomes

From the 1950s through the mid-1970s, thousands of U.S. service members were exposed to chemical and biological agents through a series of human-exposure experiments.[2] The tests took place across several branches of service and were focused on developing defensive chemical warfare capabilities such as tests of protective clothing, respiratory masks, and the impact of various agents on the operational readiness of military personnel. Tests were done on "soldier volunteers" and generally involved one or two exposures to a single agent. However, participants were often involved in multiple experiments with different agents. Most experiments began with "range finding" doses, followed by doses estimated as acute but safe.[2]

Although these programs were interested in short-term effects, thousands of veteran participants have recently voiced concerns about the possible long-term health consequences of these exposures.[1,2] Clinical evaluation of potential long-term health effects has been difficult in many cases because the lack of adequate test records and the lack of continuous health histories of participants.

Despite the lack of completeness in the test records from exposure experiments, several reviews of the health of veterans who participated in these exposure experiments have been conducted by the National Research Council/National Academies of Science (NAS) and the Institute of Medicine. Additionally, studies related to relevant exposures were also evaluated for potential chronic effects of exposure. The findings of these studies are summarized in more detail below.

3.1 Biological Agents and Vaccines

The U.S. Department of Defense conducted two separate tests called Operation Whitecoat and Project Shipboard Hazard and Defense (SHAD) to evaluate human vulnerability to biological warfare agents.

Operation Whitecoat

Operation Whitecoat began in 1954 with mostly Seventh-Day Adventist (SDA) draftees who were trained as medics but whose religious convictions forbade combat.[384] Over 2,300 SDA volunteers participated in these studies. An estimated 150 studies were conducted to clarify the disease processes and to develop and test vaccines. The biological agents tested, included: Q fever (*Coxiella burnetii*), *Francisella tularensis* (tularemia), Pseudomonas endotoxin, Staphylococcus aureus enterotoxin B (SEB), Venezuelan Equine Encephalitis virus and sandfly fever.

Vaccines against plague (*Yersinia pestis*), Adenovirus, Yellow Fever, Rift Valley Fever and Chikungunya were also tested (See Table 16.)

An assessment of self-reported health effects among 358 volunteers who served in Operation Whitecoat was conducted in 2005 by Pittman and collegues.[1] This study found no conclusive, statistically significant evidence of adverse health effects of exposure to investigational agents. There was a slightly higher frequency of asthma among subjects exposed to antibiotics or other inactive substances compared to control subjects. A borderline higher frequency of asthma and headaches were also reported among subjects exposed to tularemia vaccines.[1] Several limitations of the study were reported. Due to the small sample size of the study population, statistical associations were difficult to conclude. There was also a lack of laboratory studies and medical record reviews. Further confounding the study were volunteers having multiple exposures

Table 16. Biological Agents and Vaccines Tested on US Military Personnel

Biological Agents and Vaccines	Program	Year(s)
Pseudomonas endotoxin	Whitecoat	1954 – 1973
Sand-Fly Fever	Whitecoat	1954 – 1973
VEE	Whitecoat	1954 – 1973
VEE Vaccines	Whitecoat	1954 – 1973
EEE Vaccines	Whitecoat	1954 – 1973
WEE Vaccines	Whitecoat	1954 – 1973
Yersinia pestis (Plague Vaccine)	Whitecoat	1954 – 1973
Adenovirus Vaccine	Whitecoat	1954 – 1973
Yellow-Fever Vaccine	Whitecoat	1954 – 1973
Rift Valley fever Vaccine	Whitecoat	1954 – 1973
Chikungunya Vaccine	Whitecoat	1954 – 1973
Coxiella burnetii (Q-fever)	SHAD (Shady Grove)	1964 – 1965
Francisella tularensis (wet and dry)	SHAD (Red Cloud & Watch Dog); Whitecoat	1966 – 1967
Francisella tularensis (Schu 4)	SHAD (Shady Grove)	1964 – 1965
Plasmodium vivax (vivax malaria)*	Stateville Penitentiary (U.S. Army, State Department, U Chicago)	1940s
Staphylococcus aureus enterotoxin B (SEB)	SHAD (DTC 68-50); Whitecoat	1968
Salmonella typhi (Typhoid Fever)		
Rocky Mountain Spotted Fever		
Clostridium botulinum (Botulism)		

* This trial was conducted by a consortium that included the U.S. Army, but exposures were done on prisoners, not on U.S. military personnel. Credit Pittman (1), Brown (3)

to different agents, making statistical associations of poor-health outcomes to specific agents challenging.

Biological Weapons and Countermeasures Program at Fort Detrick, Maryland

Pittman and colleagues also conducted an assessment of long-term health effects of multiple vaccine exposures in a group of 155 multiply immunized individuals who participated in a biological weapons and countermeasures program between 1943 and 1969.[385] Participants were not military members but were employees, such as lab technicians, at Fort Detrick, Maryland. Pittman's study of these individuals involved both self-reported health effects and laboratory findings. Although this study did not involve military members, it does address some of the confounding factors seen in the Project Whitecoat assessment, such as multiple exposures and lack of laboratory studies.

No association was found between multiple vaccinations and disease; however, statistically significant changes in blood chemistry (serum calcium, serum bicarbonate, and percent thyroxine uptake) and hematology (mean corpuscular hemoglobin, mean corpuscular volume, and mean platelet volume) were identified.[384] None of these abnormalities were clinically significant or in support of the diagnosis of disease. Fatigue was the only self-reported symptom of statistical significance but was not associated with number of injections, number of vaccines, or time in the program.[384] The most significant finding of this study was the increase in prevalence of monoclonal proteins. These immunological proteins are produced by plasma cells and usually do not indicate disease; however, they can sometimes progress to disease over time, including some forms of blood cancer.[384] Although further descriptions of this condition were lacking, the authors note that further investigations of this topic are important.

Project Shipboard Hazard and Defense (SHAD)

Between 1962 and 1972, more than 5,800 military personnel participated in a series of tests as a part of the Department of Defense chemical and biological warfare defense program.[386] These tests, known as SHAD (Shipboard Hazard and Defense), were "designed to evaluate the effectiveness of shipboard detection and protective procedures against chemical, biological, or nuclear attacks." [3] Test ships and their crews were potentially exposed to agents such as Q-fever, tularemia, and Staphylococcus aureus enterotoxin B (See Table 16.)

In 1998, the Department of Veteran Affairs (VA) requested that the Institute of Medicine (IOM) review the entire medical and scientific literature on long-term health effects potentially related to project SHAD participation.[387] The IOM had access to an abundant scientific literature, published over more than five decades, including significant data from human experimentation.

The IOM literature review found the following potential health effects for biological agents *Coxiella burnetii* (Q fever), *Francisella tularensis* (tularemia), & Staphylococcus aureus enterotoxin B.[390]

1) *Coxiella burnetii* – literature indicated long-term health effects include self-limited or isolated febrile illness, pneumonia, and hepatitis
2.) *Francisella tularensis* – no significant demonstrated long-term or late developing effects found in the literature
3.) Staphylococcus aureus enterotoxin B – exposure has been implicated in certain allergic diseases like atopic dermatitis, *psoriasis vulgaris*, vernal keratoconjunctivitis, and atopic keratoconjunctivitis. SEB has also been implicated in the induction of autoimmune diseases such as Graves' disease, arthritis, and even multiple sclerosis (MS).

Beyond the literature review, the VA requested an epidemiological study to evaluate the health risks among all Project SHAD veterans in 2002.[386,3] Health questionnaires were mailed to SHAD veterans with a 60.8% return rate for participants and 46.6% for controls. To determine outcomes by specific patterns of exposure, four groups (A – D) were defined. Group C was the only group with potential exposure to active agents and thus the primary focus for this literature review. The study found no clinically significant patterns of ill health; however, SHAD veterans reported more symptoms and worse overall health than controls.[386,3] The study also found a statistically significant rate of respiratory conditions and neurodegenerative disease. Most of the neurodegenerative conditions were unspecified, making causality difficult to assign.[386] SHAD veterans also had a statistically significantly higher risk of death due to heart disease. The study was unable to find any cardiovascular risk factor data or biological plausibility to interpret this difference.[386]

In 2005, Kang and colleagues conducted a follow-up of SHAD veterans to assess mortality.[385] This study identified 4,927 SHAD participants and 10,947 non-SHAD veteran controls. Heart disease was the only cause-specific risk of mortality found among SHAD veterans.[384] The study also suggested that the increase was not specifically associated with exposure to active agents.

3.2 Anticholinesterases

Anticholinesterases were tested in a U.S. Army set of experiments at Edgewood Arsenal in Maryland. The Department of Defense also tested some nerve agents as part of their Project Shipboard Hazard and Defense.

U.S. Army experiments at Edgewood/Aberdeen

From 1955 to 1975, the U.S. Army conducted a series of experiments at Edgewood Arsenal, Maryland. These tests involved hundreds of chemical agents including several anticholinesterase agents. Approximately 1,400 volunteers were exposed to anticholinesterases including sarin (n=246), VX (n=740), tabun (n=26), cyclosarin (n=21), soman (n=83), DFP (n=11), and Malathion (n=10) at Edgewood/Aberdeen.[388] The dosage of each agent was determined by animal potency studies and subthreshold does were used for the first few test subjects. As the effects of lower doses were determined, the doses were increased and subjects were randomly assigned a low or high dose.[387] Subjects were also exposed through several routes such as intramuscular, intravenous, or inhalation. The intramuscular and intravenous studies rarely exceeded 1.5 times the incapacitating dose whereas inhalation doses were higher.

In 1980, the Department of Defense requested that an independent evaluation of the long-term health effects among the Edgewood/Aberdeen subjects be conducted by the National Research Council (NRC). According to the 1982 National Research Council review of the Edgewood/Aberdeen experiments, experimental subjects reportedly showed a wide range of symptoms consistent with *acute* cholinergic toxicity, including dizziness, frontal headache, blurred vision, lethargy, nausea, stomach pain, vomiting, rhinorrhea, chest tightness, wheezing, fasciculations, sweating on hands and feet, and significantly decreased red blood cell cholinesterase levels.[387] The 1982 NRC review of experiments involving exposure to anticholinesterases inhibitors concluded that there was no firm evidence that any of the anticholinergic test compounds surveyed produced long-term adverse human health effects in the doses used at Edgewood Arsenal.[387]

> *"On the basis of available data, in the judgment of the panel, it is unlikely that administration of these anticholinergic compounds will have long-term toxicity effects or delayed sequelae."* NRC, 1982

Project Shipboard Hazard and Defense (SHAD)

Between 1962 and 1972, as part of the SHAD project, 5,800 military personnel were exposed to select anticholinesterase and anticholinergic chemicals on a volunteer basis. Sarin and VX were the main chemical warfare agents that the men were exposed to.

As part of their 1998 review of the test information, the Institute of Medicine (IOM) focused efforts on sarin, but wrote that their findings are applicable to related organophosphate anticholinesterases, especially those in the G-series of traditional CWAs.

For organophosphorus (OP) nerve agents as a class, including military agents and related pesticides, four distinct health effects were found:

- Acute cholinergic toxicity.
- Reversible muscular weakness known as "intermediate syndrome."
- Organophosphate-induced delayed neuropathy (OPIDN).
- Subtle long-term neuropsychological and neurophysiological effects (COPIND).[4]

Gulf-War Exposures

In addition to the data from the original anticholinesterase human-exposure tests, increasing evidence suggests excess illness in Persian Gulf War veterans (GWV) can be explained in part by exposure to organophosphate and carbamate acetylcholinesterase inhibitors, including pesticides, nerve agents, and the nerve-agent symptom preventative pyridostigmine bromide (PB). Pesticides (including some organophosphates) were aggressively used in an effort to control vector-borne disease, and the Department of Defense (DoD) has estimated at least 41,000 service members may have had overexposure to pesticides.[389] Additionally, an estimated 250,000 servicemen received PB as a pretreatment to potential exposure to CWAs.[388] Potential nerve agent exposure most likely occurred during the destruction of ammunitions depots such as the one at Khamisiyah in 1991.[388] This site was later found to have housed chemical agent munitions that contained sarin and cyclosarin.[390] Small amounts of these agents were released into the atmosphere during the demolition.[389]

Veterans who exhibited reduced intellectual functioning, confusion, vestibular ataxia/vertigo attacks, and occasional disorientation were epidemiologically connected with exposure to low-level chemical nerve agent in fallout from bombing of Iraqi ammunition depots and/or PB or personal pesticide use and misuse. Krengel and Sullivan found that most veterans suffering from Gulf War Syndrome (GWS) with lowered mean-reaction times and complaints about mood were a found to have high personal pesticide use AND PB use.[391] This same group of veterans also complained more about their health than others exposed to different combinations of agents. Specifically, they noted, stiffness, muscle pain and weakness, sleep disturbance, gastrointestinal disturbances, and word-finding difficulties.[390]

In a ten-year follow-up of Gulf War Veterans, Toomey and colleagues, found that Gulf War deployment was associated with subtle declines of motor speed and sustained attention, despite

overall intact neuropsychological functioning.[392] In addition to concluding that toxicant exposures influence both these functions, these researchers found that attention was worst in those also reporting depressive symptoms.[391]

Subsequent neuroimaging studies of Gulf War Veterans indicate that there may be a nucleus of Gulf War veterans suffering from variants of a chronic encephalopathy related to different combinations of abnormal resting metabolism and cholinergic responsiveness of neurons in deep brain structures.[393,394] Additionally, recent research has provided evidence that low dose exposure to acetylcholinesterase inhibitors, including sarin, pyridostigmine bromide, and DEET, has long-term negative impacts on the memory - specifically due to hippocampal dysfunction.[395] Lastly, there is the possibility that low-level sarin exposure in the Gulf War led to increased susceptibility to sarin toxicity through decreased hydrolyzation of the agent. The mechanism of this increased susceptibility is proposed to be low blood activity of the Q isoenzyme of PON1 paraoxonase/arylesterase.

Despite these efforts to determine the cause of the complex, multi-symptom syndrome suffered by some Gulf War Veterans, documentation about exposure to organophosphate anticholinesterases is lacking or confusing (multiple exposures to different agents), which makes it difficult to link the symptoms to specific exposures.[396]

3.3 Anticholinergics

Anticholinergics were among the agents tested in the U.S. Army experiments at Edgewood Arsenal in Maryland. A total of 1,752 U.S. servicemen took part in the human-exposure trials of anticholinergic compounds. These men received 2,614 exposures, which required some men to receive multiple exposures, sometimes with different compounds (See Table 17).

Test records indicate that experimental subjects reportedly showed a wide range of symptoms consistent with *acute* toxicity, including dizziness, lethargy, confusion, combativeness, mood disorders, and hallucinations shortly after exposure.[387]

However, long-term or delayed effects of exposures were rare, and were documented.[387] One person experienced flashbacks while still at Edgewood Arsenal after receiving intravenous EA 3834.[397] Additionally, accidental exposures of two laboratory personnel to EA 3167, resulted in mild, but nontrivial, impairment of cognitive function for 6-to-12 months after exposure. After this time, an apparent full recovery ensued.[396]

When the National Research Council reviewed the Edgewood/Aberdeen human exposure experiments in 1982, they concluded that:

> *No 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.*
>
> *On the basis of available data, in the judgment of the panel, it is unlikely that administration of these anticholinergic compounds will have long-term toxicity effects or delayed sequelae.*

Table 17. Summary of Exposures to Anticholinergics

Tox Number	Agent code	No. volunteers	Total exposures*
B1	BZ (EA-2277)	292	358
B2	EA-3443	101	101
B3	EA-3580	130	133
B4	Scopolamine	534	636
B5	Atropine	444	738
B6	EA-3167	2	4
B7	Ditran	9	13
B8	EA-4929 (benzetimide)	18	18
B9	27349	50	50
B10	226,086	21	21
B11	302,196	52	56
B12	301,060	29	29
B13	302,282	8	8
B14	302,368	5	5
B15	302,537	18	18
B16	302,668	39	39
B18	Benactyzine	16	26
B21	M-Scopolamine	72	114
B22	M-Atro; (atropine methyl nitrate)	18	50
B23	EA-3834	144	173
B25	TAB	24	24
Total Anticholinergics		1,752	2,614

*Some volunteers received more than one chemical or exposure

As part of the National Research Council's review of the human exposures tests, a survey was devised for self-reporting of health status.[4] More than eighty percent of the veterans who received a survey completed it, and of the respondents exposed to anticholinergic agents, almost ninety percent reported no health problems related to experimental exposures, and seventy-nine percent reported good-to-excellent health.[4]

The NRC also notes that data is lacking on many of the anticholinergic compounds tested to determine whether the substance is the cause of longer-term health effects such as flashbacks and transient cognitive impairment.[4] They also note that subjects were not kept under long-term observation to determine if the compounds indeed had delayed or prolonged effects. There are no recent studies examining the long-term effects of anticholinergics specifically on military populations, so a comparison between the historical analyses and more recent ones cannot be made.

3.4 LSD, Other Classical Hallucinogens, & Lysergamides

From 1955 through 1967, the U.S. Army Chemical Corps and the U.S. Intelligence Corps conducted human experiments with LSD.[398] There were 741 soldiers recorded as exposed to LSD. Subjects were given between one and five doses ranging from 0.4 to 75 micrograms per kilogram each. Most (63%) subjects were given only one dose which averaged 1.0 to 1.5 micrograms per kilogram.

U.S. Army Medical Department Analysis

In 1978, the U.S. Army Medical Department conducted a follow-up study to evaluate the 741 individuals who were "believed to have received LSD in Army experiments".[397] Health evaluations were done to identify possible long-term health effects for 220 exposed subjects. An additional 100 subjects were evaluated using a "Health History Questionnaire" after declining medical examination. A matched control group was not obtained due, in part, to the bias in initial volunteer selection. The LSD subjects were not a random selection of the Army population due to strict physical and psychological screening. These subjects were also of higher intelligence and greater overall health than the average Army soldier or the general population. Additionally, many of the subjects were involved in other experiments, exposing them to more than one chemical/biological agent and further confounding agent-specific long-term health impacts.[397, 3]

Of the 320 subjects evaluated, 281 were positively identified as having received LSD.[397] Of the 320 LSD subjects evaluated, 76 (24%) reported one or more long-term adverse reactions to LSD exposure. Flashbacks were the most common adverse reaction followed by somatic complaints, depression, personality changes, and anxiety. Less common reactions included nightmares, paranoid ideation, dissociative episodes, phobia, memory loss, drug abuse, and psychosis. [397,3]

- *Flashbacks*. At the time of this medical follow-up, flashbacks were thought to be one of the most common adverse effects of hallucinogen use.[399] Twenty-seven (8%) out of 320 subjects reported flashbacks. Most subjects reported that the onset of flashbacks occurred within the two years of LSD exposure. The reported flashbacks were similar to those described in other LSD literature of the time with the exception of their unusual persistence. Flashbacks continued to the present time (18 years after LSD exposure) for more than 40% of subjects who reported flashbacks. The prevalence of flashbacks varied widely depending on the population studied.[400,401] Individuals administered in a therapeutic or volunteer research setting are less likely to have flashbacks than illicit LSD users.[402] Strassman attributed this lower incidence to a well-controlled environment: "individuals (both normal volunteers and patients) are carefully screened and prepared,

supervised and followed-up, and given judicious dose of pharmaceutical quality drug." [403] Since this time population-level studies of hallucinogen users have found no adverse long-term sequelae associated with use.[280,281,282]

- *Somatic complaints.* Somatic complaints such as headache, weakness, shortness of breath, and allergies were reported as adverse effects from LSD exposure by 18 (6%) subjects. [386] Most somatic complaints were reported to have an onset two years post exposure. In most cases, the somatic complaints were attributed to other causes and commonly occur in healthy subjects with no chemical exposures.

- *Depression.* Depression was reported as an adverse effect of LSD exposure in 12 (4%) subjects.[386] The onset of depression ranged from a few days post exposure to several years. Although depression has previously been reported as a reaction to LSD[404], the exposed veterans did not report an excess of depression greater than what is seen in the general population. The most severe outcome of depression is suicide. Cohen reported suicide as an adverse outcome related to LSD use; however, those cases were reported in a group of psychiatric patients undergoing therapy.[403] In this study, one subject who reported severe depression attempted suicide two years post exposure but remained asymptomatic after receiving psychotherapy. Suicide gesture or suicide ideation was reported for an additional 3 subjects who experienced depression.[386]

- *Personality changes.* Previous studies indicate that personality changes are a common self-reported adverse effect after LSD use.[389,405] In the Army follow-up study, seven (2%) subjects reported personality changes that they attributed to LSD exposure. Most reported negative changes such as social withdrawal, loss of interest in work, irritability, and aggressiveness. Positive personality changes (i.e., self-awareness, tolerance, etc.) were observed in two subjects. The pre-LSD psychological examinations where not available for review, making it difficult to compare and distinguish personality changes among LSD exposed subjects.

- *Anxiety & nightmares.* LSD ingestion is frequently followed by episodes of anxiety, especially in individuals with rigid, structured personalities where the threatened loss of self-control causes severe stress.[399,403,404] Six (2%) subjects reported sporadic recurrent anxiety as well as prolonged constant increases in anxiety. None of the subjects reported anxiety severe enough to require hospitalization. Nightmares were also reported by five (2%) subjects. Due to the lack of information on LSD exposure and nightmares, they were suspected to be closely related to underlying anxiety.[397]

- *Paranoia*. Paranoia has been described as a short-term adverse reaction of LSD ingestion.[403] As with reports of anxiety after LSD exposure, paranoia is often reported in those individuals with rigid personalities that feel threatened by the loss of control.[403] In the review of Army studies, 4 (1%) subjects reported paranoid ideation as a long-term adverse reaction. Two of these subjects indicated that their paranoia resolved after several years post LSD exposure.

- *Dissociative episodes & Memory loss*. Dissociative episodes and/or memory loss are adverse reactions rarely mentioned in LSD literature; however, dissociative episodes were reported by five (2%) subjects and memory loss by four (1%). Dissociative episodes occurred anywhere from a few days post exposure to several years post exposure. The dissociative episodes in three subjects were triggered by alcohol. In two subjects, memory loss was attributed to the normal aging process.

- *Phobic neurosis & Illicit drug use*. These conditions are rarely discussed in the LSD literature. Two (>1%) subjects reported severe phobias after LSD ingestion that has persisted to the present time.[397] Although LSD is not known to be addicting,[399] two (>1%) subjects reported experimenting with other drugs as a result of LSD exposure.[397]

- *Prolonged psychosis*. Prolonged psychosis is one of the most common adverse reactions reported after LSD exposure and is estimated to occur in 0.8 per 1,000 experimental subjects.[397,398] In this study, only one subject reported prolonged psychosis as an adverse effect of LSD exposure. The subject required hospitalization where he was given tranquilizer medication to resolve symptoms.

National Research Council/National Academy of Sciences Analysis

In 1985, the National Research Council (NRC) conducted a health survey for soldiers involved with LSD experiments at Edgewood/Aberdeen.[4] In the 1980 U.S. Army Medical Department follow-up study, 741 soldiers were believed to have received LSD;[397] however, only 571 were positively identified as having received the drug. Of the 571 soldiers who were identified as exposed to LSD, 317 (56%) responded to the National Research Council survey. The survey asked multiple health-related questions, and, based on the results, the LSD -exposed subjects did not differ significantly from controls in terms of total hospital admissions, admissions for malignant neoplasms, mental disorders, or current health status.[4] Overall, the NRC study was consistent with the findings of the 1980 Army LSD Follow-up study.[3] The NRC health survey did find a statistically significant increase in first admissions for nervous system and sense organ disorders.[4] It was noted that those admissions were small, and no LSD dose relationships were found. There was no evidence of an increase in suicide or epilepsy; however, subjects reported increased use of controlled substances subsequent to these experiments.[3,4]

3.5 Oximes, Irritants, & Incapacitants

Oximes

The warfare potential of chemical agents grew rapidly during and after World War II.[406] Research on lethal nerve agents was quickly followed by the development of treatment methods.[405] Due to their effectiveness in treating organophosphate poisoning in animals, the U.S. Army tested oximes in soldier volunteers from 1958 to 1975 at Edgewood, Maryland.[405]

The three oximes Toxogonin, Trimedoxime (TMB-4), and, Pralidoxime methane sulfonate (P2S) were tested on a small number of subjects. Toxogonin was administered to 41 subjects either intravenously (0.5-1.0 µg/kg or 60-128 mg infused with aminohippuric acid), orally (1-9 g), or intramuscularly (2.5-10 mg/kg). TMB-4 was administered to 32 subjects; however, the route and dose were not determined due to lack of data as well as subjects being given other potent drugs at the time of administration. P2S was administered to 95 subjects either intravenously (5 mg/kg), orally (2-9 g or 1-3 g before nerve agent), or intramuscularly (1-2 g after nerve agent).

According to the 1984 National Research Council review of the Edgewood experiments, several acute symptoms were reported by test subjects including dry mouth, blurred vision, lethargy, tingling sensation, dizziness, eye discomfort, nausea, etc.[405] These symptoms were moderate and resolved within 24 hours in all but one subject. This is consistent with the finding that the oxime compounds are eliminated rapidly from the body, and adverse health effects are short-lived and reversible. The NRC review concluded that there was no firm evidence that any of the oxime test compounds studied produced long-term adverse health effects in the doses used. It was also noted that there was very little research available; therefore, a conclusion was not reached regarding carcinogenicity, mutagenicity, teratogenicity, or reproductive anomalies associated with oximes.

Irritants

Irritants, also called riot control agents, were used to dispel rioters in Paris before World War I (WWI) and by French and German soldiers during that war. CA, CN, and DM were used in hand grenades, mortar rounds, and artillery shells for harassment and casualty functions.[407] After WWI, the United States Chemical Warfare Service focused on further developing "harassing agents" CN and DM followed later by CS. The United States used CS extensively in the Vietnam War to clear enemy personnel from congested areas and to prevent civilian casualties. The use of riot control agents in Vietnam didn't go without controversy. In early 1975, the United

States acknowledged riot control agents as prohibited war gasses and renounced their use in Vietnam.

Riot control agents are still used worldwide by law enforcement agencies for the purpose of crowd and riot control as well as by military personnel in combat and training to simulate the efficacy of protective measures in event of chemical attack.[406] CN is also used in self-protecting devices labeled as Mace. In general, riot-control agents are designed to have a rapid onset of effects, produce a high degree of immediate disability, and require a short recovery time as soon as the rioters are dispersed from the area.[406,408] Several irritants were tested as part the U.S. Department of Defense human exposure experiments as part of its chemical and biological warfare defense program in Edgewood, Maryland.[405] The tests focused on short-term effects on health; however, questions concerning their possible long-term effects have raised concerns.[3,4] The National Research Council conducted a review of the Edgewood experiments which is described below.

Bromobenzyl cyanide (CA)

The lacrimatory chemical bromobenzyl cyanide (CA) was studied on 13 subjects at Edgewood in 1966. CA was studied due to its persistence in enclosed areas over lacrimators CS and CN.[405] CA exposure ranged from 0.9 to 204 mg-min/m3 for a time of 50 seconds to 10 minutes. Each subject was only exposed once, and they wore masks upon entry to the aerosol chamber until the CA concentration had equilibrated. Adverse effects such as ocular irritation followed by conjunctivitis and upper respiratory tract irritation with rhinorrhea were transient.[405,3] Laboratory analysis done for 12 subjects, 7 days after exposure, showed one subject with minimal leukocytosis (WBC 12,800) not seen before exposure.[405,3]

The National Research Council review of the Edgewood experiments found CA unlikely to produce long-term health effects after exposure at the doses and duration used at Edgewood. [405]

Chloroacetophenone (CN)

CN was tested on 99 subjects at Edgewood between 1958 and 1972. Subjects were exposed by either dermal application or by aerosol (they entered masked and removed the masks after CN concentration had equilibrated).[405,3] For aerosol-exposed subjects with known exposure data, concentrations ranged from 6-315 mg·min/m3 with exposure times between 0.15 seconds to 3.36 minutes.[405] Aerosol-exposed subjects were exposed between one and five times. The dermal exposed subjects, for whom exposure data was known, were given 0.01-0.025 ml of CN to their bare or clothed arms.[405] Adverse effects of aerosol exposure included ocular irritation, respiratory irritation, skin irritation, headache, and dizziness. Most symptoms were transient

and resolved minutes after removal of the agent. Only one of the dermal exposed subjects experienced erythema that lasted 7 hours at exposure site.[405,3]

The National Research Council review of the Edgewood experiments found no evidence of lasting ocular or respiratory effects in subjects exposed to CN. Overall, exposures were short with low-doses and recovery was complete within minutes.[405,3]

Adamsite (Diphenylaminechloroarsine, DM)

Ninety-six subjects were exposed to DM aerosol at Edgewood in either 1958 or between 1966 and 1968. Subjects tested in 1958 underwent between one and five exposures; dose and exposure times ranged from 7.1 to 100 mg·min/m3 and 1 minute to 4 minutes 28 seconds respectively.[405] The subjects tested between 1966 and 1968 were only exposed once with a dose between 7.1-236 mg·min/m3 for 45 seconds to 10 minutes.[405,3] The most common adverse health effects were respiratory tract irritation including burning sensations of the respiratory passages, choking sensations, dysphonia, dyspnea, coughing, sneezing, and nausea[405] Most were transient and only lasted for a few hours after removal from the agent.

The National Research Council review of the Edgewood experiments found DM to have a greater acute toxicity to the respiratory tract than CS and CN.[405,3] Health effects were transient and subjects recovered quickly. The review stated that DM is unlikely to produce long-term health effects after exposure at the does and duration used at Edgewood.

Nonanoyl morpholide

Thirty-two subjects were exposed to nonanoyl morpholide in an aerosol chamber at Edgewood in 1958.[405] Some of the subjects wore protective masks during exposure. Exposures ranged from one to four times with duration of 10 seconds to 8 minutes. The doses were not known. Adverse health effects such as respiratory tract irritation, nausea, vomiting, and headache were mostly transient; however, one subject experienced a headache for one-week post exposure.[405,3]

The National Research Council review of the Edgewood experiments concluded that no long-term health effects in subjects tested with nonanoyl morpholide would be expected. [405]

Chlorobenzylidene malononitrile (CS)

CS experimental tests were performed on human subjects from 1958 to 1973 at Edgewood. Tests included 1,073 subjects exposed to aerosolized CS, 180 subjects with skin applications, 82 subjects with skin and aerosol exposures, and 31 subjects underwent applications to their eyes.[405] There was a wide range of dosages used (from 0.03 to 345 mg·min/m3). Higher doses

were used in tests of equipment. Complete experiment records were available for 105 CS test subjects representing a cross-section of CS protocols used. Adverse health effects due to CS exposure included lacrimation, eye irritation, upper respiratory passage irritation, chest constriction, and dyspnea.[405,3] No effects were noted in the skin application subjects for whom records were available.

Pre-exposure and post-exposure laboratory analyses were done on 72 subjects.[405] Laboratory abnormalities were noted in 11 subjects post-exposure. Seven subjects had urinary sediment containing 2-10 white cells per high-power field with no reports of a lower urinary tract source of white cells. Their post-exposure renal-function tests were normal. An additional 3 subjects had high serum glutamic-oxaloacetic transaminase (112, 38, and 31 IU). In one subject, leukocytosis accompanied the marked increase in transaminase. Leukopenia was noted in one additional subject.

Two additional studies were conducted utilizing CN in conjunction with other chemical agents. Thirty-one subjects were exposed to either 0.1% or 0.25% CS in water with 0.5% polysorbate 20 or 0.05- 1.0% CS in trioctyl phosphate in their right eye.[405] Subjects reported intense ocular irritation and lacrimation with one subject having corneal staining as seen with a slit lamp. All adverse effects resolved within 24 hours post exposure.

CS was also used to determine the effects of skin pigment on susceptibility to sensitization, sensitizing and irritating concentrations of CS, and cross-sensitization with CN.[405] Eighty-six skin applications of 0.01% and 0.1% CS were conducted.[406] The results of those applications were available for 45 cases and concluded that lighter skin subjects seemed more susceptible to sensitization and previously CS-sensitive subjects showed no cross-reactivity to CN. Primary irritation dermatitis was also noted for several subjects exposed to 0.1% CS but not to 0.01% CS.

The National Research Council review of the Edgewood experiments concluded that repeat exposures to CS may cause allergic contact dermatitis and may induce idiosyncratic hepatitis or allergic pneumonitis; however, these effects seem reversible and not likely to become chronic in the absence of repeat exposures.[405,3]

Benzylidene malonitrile

Nineteen subjects were experimentally exposed to benzylidene malonitrile at Edgewood. Most (80%) subjects had two exposures, but the doses were not available. Subjects experienced chest constriction and dyspnea as a result of exposure. Due to the lack of follow-up information, the National Research Council concluded that long-term health effects were not possible to predict.[405]

2-Bromoethyl-bromoacetamide

Subjects were exposed to 2-bromoethyl-bromoacetamide at Edgewood in either 1963 (2 subjects exposed) or in 1969 (15 subjects exposed). The two subjects exposed in 1963 were given a single dose each of 39 and 57 mg·min/m3. No effects were described after exposure. 2-Bromoethyl-bromoacetamide was further tested in 1969 on 15 subjects with one exposure each ranging from 29.8 to 65.8 mg·min/m3.[405] Adverse health effects included irritation of the eyes, nose, throat, and periorbital sites. The post exposure laboratory results were normal. Due to the lack of follow-up information, the National Research Council concluded that long-term health effects were not possible to predict.

Dibenzoxazepine (CR)

CR was studied as a potential replacement for CS as it has a lower toxicity than either CN or CS and its effects are generally the same as those of CS, although it is more potent a tear agent. A total of 97 subjects were exposed to CR at Edgewood between 1963 and 1972. Thirty-three subjects were exposed to aerosolized CR at a concentration ranging from 0.01-34 mg·min/m3 for a duration of 1 second to 6.75 minutes. Only one subject had two exposures. Adverse health effects experienced after exposure to CR aerosol were transient in nature and were mostly respiratory and ocular related.[405,3]

An additional 24 subjects were exposed through open patch testes where 0.1 or 0.25-1.0% CR was applied to their foreheads, faces, necks, and hands for 5 or 30 minutes. Closed patch tests were also done on 20 subjects with 0.01, 0.1, or 0.25-1.0% CR applied to their foreheads for 5 or 30 minutes. Adverse health effects from patch exposures were listed as stinging and erythema at the exposure sites and resolved within 24 hours.[405,3]

An aerosol chamber was used to test an additional 11 subjects who were wearing protective masks. Concentrations of the CR spray was available; however, CR was sprayed on the test subjects faces from 3 or 12 feet for 10 seconds, and the exposed areas were then washed. Adverse health effects seen after exposure were skin irritation at the exposure site, lacrimation and conjunctivitis, upper respiratory tract irritation, and numbness at the exposure site.[405,3]

The National Research Council concluded that the small number of exposures to CR at low doses were unlikely to cause long-term health effects in subjects exposed to CR.

1-Methoxy-1,2,5-cycloheptatriene (CHT)

Between 1969 and 1970, 16 subjects were exposed to CHT in an aerosol chamber at Edgewood. Subjects were each exposed once to 15.4 to 64 mg·min/m3 of CHT aerosol for 30 seconds to 5

minutes. Adverse health effects were reported as dermal irritation as well as eye irritation, causing incapacitation due to eye closure and blurred vision.[405,3] One subject reported "chest congestion." The effects of exposure were resolved within 15 of leaving the chamber.

Laboratory analysis was done on the subjects 9 days after exposure. Two subjects had slight abnormalities in SGOT (serum glutamic oxaloacetic transaminase) after exposure to CHT and may have represented idiosyncratic hepatic reactions to the chemical. One subject showed an increase in alkaline phosphatase while another subject showed a decrease in hemoglobin after CHT exposure.[405]

The National Research Council review was unable to relate those abnormalities with exposure. They also concluded that long-term health effects of the exposure were difficult to predict given the available information.[405]

Chloropicrin (PS)

Chloropicrin (PS) was tested on 136 subjects at Edgewood, MD between 1955 and 1971.[405] Test subjects wore gas masks and remained in a test chamber for up to four hours. No dosages were available. Minimal gas-mask leakage was reported in test subjects, and there were no acute adverse health effects reported after exposure. The National Research Council review of the Edgewood experiments found PS unlikely to produce long-term health effects in volunteers exposed at Edgewood.[405] The NAS analysis did not recount exposure information to any of the other substances treated in this report.

Incapacitants

Psychochemical incapacitants were of interest to the U.S. Chemical Corps for use in overcoming an enemy without the need for human misery, destruction or killing typically seen in warfare. Edgewood scientists were tasked with evaluating the biologic effects of a variety of chemicals that could affect the brain to alter the state of mind or mood. Several psychochemical irritants were tested as part the U.S. Department of Defense human exposure experiments in Edgewood, Maryland. The tests focused on short-term effects on health; however, questions concerning their possible long-term effects have brought concern.[405,3] The National Research Council conducted a review of the Edgewood experiments and a review of the findings is described below.

Phencyclidine, PCP

In the late 1950s, the Army began testing phencyclidine on volunteer subjects at Edgewood.[405] some studies were similar to those found in non-military research at the time. These studies

included seven subjects, who underwent a water loading test. Subjects treated with phencyclidine at 0.1 mg/kg before a saline infusion showed evidence of inhibition of antidiuretic hormone secretion. Another study involved oral administration of 5 and 10 mg of SNA after which subjects were asked to walk on a treadmill in a heated room (100° F). In general, the doses of SNA given to subjects had no impact on the exercise-induced heart-rate changes, metabolic rate, evaporative heat losses, or tolerance times.[405]

Edgewood experiments went beyond civilian research of phencyclidine by administration of phencyclidine by inhalation. An inhalation chamber was used to disperse SNA in a methylene dichloride solution. Concentrations were varied to achieve a steady dose of approximately 100 µg/kg. With a dose range of 25-62 µg/kg, subjects had feelings of unreality, involuntary eye movement, and mood changes. At 100 ug/kg, subjects experienced visual disturbances, blurred vision, ataxia, limb paraesthesias, memory impairment, and became noncommunicative. Analgesia, nausea, and vomiting developed rapidly between 100 and 180 µg/kg. Four subjects were exposed to the largest dose of 225 µg/kg. Collapse and prostration occurred in three of those subjects and incapacitation was observed in the fourth. In general, test subjects had short lived adverse health effects of exposure, lasting 6 to 8 hours; although at the highest doses symptoms persisted for 24 or 48 hours for some subjects.[405,3]

The National Research Council review concluded that it is unlikely that detectable long-term or delayed effects have occurred or will occur in the subjects exposed to phencyclidine at Edgewood. Their conclusions were based on the doses and frequencies of exposure to phencyclidine in addition to the small number of test subjects. Forty-eight (56%) of the 86 subjects exposed to phencyclidine returned the NRC follow-up survey.[4] The survey found that the phencyclidine exposed group had the lowest proportion of volunteers ever hospitalized, but that their primary health concerns were mental disorders. [405,3]

Dibenzopyrans

Edgewood experiments using dimethylheptylpyran and its derivatives in humans, spanned the period from 1958 through 1968. One of the earlier studies involved a mixture of dimethylheptyl pyran isomers given to 35 subjects at 0.5-4 mg per 70 kg of body weight. Adverse health effects were generally dose-related and included hypotension, tachycardia, decrease in oral temperature, visual disturbance, subjective symptoms of thirst and dry mouth, and decreases in motor performance. At 2 mg of dimethylheptylpyran, subjects were noted to be incapable of performing their regular military duties. [405]

Between 1963 and 1966, 100 subjects were administered doses of a dimethylheptylpyran acetate racemic mixture either orally, intravenously, or intramuscularly. Oral doses ranged from 3 to 60 µg/kg. Intravenous doses ranged from 0.5 µg/kg to (in a few subjects) 5 µg/kg. Intramuscular doses were between 0.5 and 5 µg/kg. Some subjects experienced tachycardia and orthostatic hypotension at almost all doses. These the cardiovascular effects disappeared in most subjects after 24 hours. Decreased body temperature, dryness of the mouth and throat, nasal stuffiness, apathy, and nausea were also reported; however, their intensity was dose-related.[409]

Approximately 125 subjects were exposed to eight optical isomers of dimethylheptylpyran acetate given singly or in combination. Six of the isomers had little biologic activity, and subjects appeared unaffected except for pain at injection site. Two of the isomers had significant biological activity and produced intense tachycardia and orthostatic hypotension in subjects given 1-2 mg intravenously. [405]

Both hepatic and renal functions were assessed during the dimethylheptylpyran studies, and occasional borderline abnormal results noted after exposure. Upon follow-up, these abnormalities did not appear to be clinically significant. EEG and ECG assessments were also done to follow the intensity and duration of any drug-induced changes in cardiovascular and brain functions. Upon evaluation the effects did not appear to be particularly specific or clinically significant for acute or long-term toxicity. [405]

Although the dibenzopyrans produced potent long-lasting orthostatic hypotension during the Edgewood experiments the National Research Council review did not have enough information to determine the plausibility of chronic effects. It was noted that there was no indication from the responses on the National Research Council follow-up questionnaire that the current health of exposed subjects was affected. [405]

No further information on military exposures and health outcomes was found for any of other of the incapacitants tested on volunteers.

3.6 Sulfur Mustard

National Research Council analysis of experiments that took place at Edgewood looked at the health status of the 147 soldier volunteers who were exposed to sulfur mustard between 1955 and 1966.[405] The majority of soldiers exposed (n=116) wore gas masks into an aerosol chamber to test the effectiveness of protective attire. Subjects were exposed up to 14 times over various days and were removed from the test if their protective garments became compromised. Exposures ranged from 14 to 60 minutes with a Ct (product of concentration and duration of exposure) ranging between 2,031 mg·min/m^3 and 30,800 mg·min/m^3.

An additional 31 subjects underwent cutaneous exposure to test the effectiveness of antidotes. Twenty subjects were exposed to sulfur mustard on their arms, either in a 4 mg drop on their forearms or 2 g/10 cm^2 on three separate swatches of protective cloths taped to their arms. Eleven subjects were exposed to 1,100 mg·min/m^3 of moving sulfur mustard vapor at the same site (seven daily exposures), followed by 200 mg·min/m^3 of static sulfur mustard vapor at a different site (three daily exposures). Of the 147 exposed subjects, 59 had no reaction, 77 experienced erythema without blistering, and 11 experienced skin blistering. All of the subjects who experienced blistering were subjects with dermal exposure. Two of the subjects with blisters were hospitalized. No ocular or respiratory tract injuries were reported.[405406]

The National Research Council concluded:

> "Serious long-term adverse effects in the small number of soldiers who received one or a few low-dose exposures at Edgewood seem unlikely."

Some of those exposed at Edgewood suffered skin injuries that took several weeks to resolve. However, in view of the small number of persons tested, and the very low dosages involved, it is unlikely that a statistically significant increase in the risk of cancer or other chronic disease can be detected in those exposed to sulfur mustard gas at Edgewood.[4]

Sulfur Mustard in Iran-Iraq War

During the Iraq-Iran war, the Iraqi army used an estimated 1,800 tons of sulfur mustard against Iranian soldiers and civilians, resulting in over 100,000 people with mustard-related injuries.[108] The long-term sequelae experienced by Iranian veterans are summarized in the front section of this paper and this summary includes information of sequelae amongst civilians exposed to sulfur mustard during the war or in the course of military operations.

3.7 Dioxins

From 1962 through 1971, the U.S. military sprayed an herbicide defoliant in southern Vietnam as part of Operation Ranch Hand.[409] Several different tactical formulations were used, and the code names Orange, Blue, White, Pink, Green, and Purple were used to identify the herbicide used.[410] Agent Orange was the most widely used herbicide during Operation Ranch hand.[413] Agent Orange was composed of a 1:1 mixture of 2,4- dichlorophenoxyacetic acid and 2,4,5-tricholorophenoxyacetic acid. During the manufacture of the latter, 2,3,7,8- tetracholorodibenzo-p-dioxin (TCDD), also referred to as dioxin, was formed as a contaminant.[408] After the Vietnam War ended, veterans expressed concerns about how exposure to herbicides including Agent Orange, and their dioxin contaminant, had affected their health.[408,411]

The U.S. Department of Veterans Affairs and other U.S. governmental organizations, such as the Institute of Medicine and the National Academy of Science (NAS) in collaboration with the Centers for Disease Control and Prevention, were tasked with conducting research studies on possible health effects of Agent Orange exposure on U.S. veterans.[412] This collaboration produced the report "Veterans and Agent Orange" in which they found "sufficient evidence" to associate Agent Orange exposure with the following diseases: soft tissue sarcoma (including of the heart), non-Hodgkin's lymphoma, chronic lymphocytic leukemia (including hairy cell leukemia and other chronic B-cell leukemia), Hodgkin's disease, and chloracne.[410,411,413]

They also determined there is "limited/suggestive evidence of association" found with laryngeal cancer; cancer of the lungs, bronchus, or trachea; prostate cancer; multiple myeloma; AL amyloidosis; early-onset peripheral neuropathy; *porphyria cutanea tarda*; Parkinson's disease; hypertension; ischemic heart disease; type 2 diabetes (mellitus); and spina bifida in offspring.[410,411]

Given these presumptive associations due to Agent Orange exposure, the Department of Veterans Affairs released a statement on November 1, 2010 that VA disability benefits will now be paid for the following: acute and subacute transient peripheral neuropathy, chloracne, chronic lymphocytic leukemia, diabetes mellitus (type 2), Hodgkin's disease, multiple myeloma, non-Hodgkin's lymphoma, *porphyria cutanea tarda*, prostate cancer, respiratory cancers, soft tissue sarcoma (other than osteosarcoma, chondrosarcoma, Kaposi sarcoma, or mesothelioma), AL amyloidosis, B-cell (hairy cell) leukemia, Parkinson's disease, and ischemic heart disease.[414] Several studies have been conducted since the Agent Orange Act, and are included in updates of the "Veterans and Agent Orange" report. Below are summaries of studies relevant to the potential for long-term sequelae in military servicemen.

Prostate cancer

Chamie et al. studied the association between Agent Orange and prostate cancer among northern California Vietnam veterans.[415] In this cohort study, a veteran was classified as being exposed through self-reported exposure to Agent Orange on the initial application for medical benefits and was stationed in known areas that were sprayed with Agent Orange during 1962 through 1971. A total of 6,214 men were classified as exposed whereas 6,930 were classified as not exposed to Agent Orange. They found that patients exposed to Agent Orange were twice as likely to develop prostate cancer as patients who were unexposed (OR, 2.19; 95% CI, 1.75-2.75; P <0.001). Chang and colleagues stated that the self-report exposure estimates used by Chamie led to profound exposure misclassification.[416] They commented that misclassification combined with potential selection bias largely invalidates the findings of the Chamie study and cannot associate Agent Orange/TCDD exposure and prostate cancer risk.

Myeloma

Parikh and Pearlman conducted a case-control study to estimate the risk of being diagnosed with multiple myeloma and AL amyloidosis after exposure to Agent Orange in a clinical population of military veterans at the Department of Veterans Affairs Medical Center in Memphis, TN.[410] Military veterans with Agent Orange exposure (n=1,873) were compared to other hospital patients in the same age group (62–73 years) without Agent Orange exposure (n = 62,122). Of the veterans exposed to Agent Orange, one (0.053%) was diagnosed with multiple myeloma and zero were diagnosed with AL amyloidosis. In unexposed patients, 34 (0.054%) were diagnosed with multiple myeloma and 3 (0.004%) were diagnosed with AL amyloidosis. The risk of multiple myeloma was nearly identical in both groups (odds ratio, 0.98; 95% confidence interval, 0.13–7.13), and statistical analyses were not performed for AL amyloidosis due the low numbers of diagnosed patients. The author did note that larger, multicenter-based studies are needed to confirm this observation.

Benign Prostatic Hyperplasia

In a longitudinal, prospective cohort, Gupta and colleagues studied 971 U.S. Air Force veterans involved in Operation Ranch Hand and 1,271 Air Force veterans who did not spray herbicides to assess the effect of serum TCDD concentration on the risk of development of benign prostatic hyperplasia (BPH).[417] The BPH risk was determined by medical record review and by medical examinations conducted during the study. The authors found that TCDD exposure at general population levels is associated with a decreasing risk of BPH with higher exposure levels. They also found that TCDD exposure was negatively associated with serum testosterone levels.

Rhabdomyosarcoma in Offspring

A case-control study to evaluate the role of parental military-related exposures to dioxin compounds and rhabdomyosarcoma (RMS) risk in offspring was performed by Grufferman.[418] The study consisted of 319 patients with RMS and 319 pair-matched controls. Overall, they found little evidence that parental military service is associated with RMS in offspring after adjusting for family income, parental education, recreational drug use, length of pregnancy, and maternal spotting, cramping, or abnormal bleeding during pregnancy. Paternal exposure to AO was positively associated with childhood RMS but was not statistically significant (adjusted OR = 1.72, 95% CI, 0.55 - 5.41). These results are consistent with other studies evaluating exposures in Vietnam veterans and the risk of childhood cancer.[417]

Respiratory Disease

Cypel and Kang examined the risk of disease-related mortality in Army Chemical Corps (ACC) veterans who sprayed herbicides in Vietnam.[419] They compared deployed Vietnam veterans with non-deployed veteran peers or U.S. civilian men. The study found that the risk of mortality from respiratory disease (malignant or nonmalignant) was significantly greater for ACC Vietnam veterans in comparison with their non-Vietnam veteran peers and U.S. civilian men. They also reported a statistically significant excess mortality from chronic obstructive pulmonary disease (RR = 4.82, 95% CI, 1.10 – 21.18).

Diabetes

Michalek and Pavuk studied diabetes in military personnel who were part of Operation Ranch Hand in comparison with a cohort of other Air Force veterans who served in Southeast Asia (SEA) during the same time period but who did not spray herbicides.[420] They calculated the relative risk of diabetes was 21% higher in Air Force Health Study participants than in the SEA comparison cohort (RR = 1.21, p = 0.16) after adjustment for BMI at follow-up and during the qualifying tour in Vietnam or SEA, family history of diabetes, smoking history in 1982, year of birth, last year of service in the Ranch Hand Unit or in SEA, ratio of the number of days spent in Vietnam to the number spent in SEA, and military occupation.

Michalek and Pavuk then postulated that Agent Orange was more heavily contaminated with TCDD earlier in the war, and sought to study those who served before 1970 versus after 1970. They reported that Ranch Hand participants who served before 1970 had a 65% higher risk of diabetes than the SEA comparison group (RR = 1.65, p = 0.005). No association with diabetes was seen in those serving after 1970 (RR = 0.85, p = 0.45). The number of days Ranch Hand participants sprayed, also played a confounding factor. Participants who had at least 90 days of spraying had a 32% higher risk of diabetes (RR = 1.32, p = 0.04). Analysis of time-to-diabetes

was applied to the individual Log (TCDD) values of all the Ranch Hand and SEA subjects generated a significant slope for diabetes incidence with serum dioxin (hazard ratio (HR) = 1.29 p < 0.001). They concluded that calendar period of service, days of spraying, and time spent in SEA are important confounders in the Air Force Health Study.[419]

Spina Bifida

Ngo and colleagues studied the association between Agent Orange exposure and the risk of spina bifida through a meta-analysis of seven studies, including 330 spina bifida cases and 134,884 non-cases.[421] Three case–control studies were identified with a total of 80 spina bifida cases, three retrospective cohort studies reported on 12,875 infants or children of exposed fathers and 103,220 infants or children of unexposed fathers, and one cross-sectional study involved 213 children of exposed fathers and 210 children of unexposed fathers.[420] All seven studies involved veteran service men. The combined relative risk for spina bifida associated with paternal exposure to Agent Orange was 2.02 (95% CI, 1.48 – 2.74), with no statistical evidence of heterogeneity across studies. Non-Vietnamese studies showed a slightly higher combined relative risk (RR = 2.22; 95% CI, 1.38 – 3.56) than Vietnamese studies (RR = 1.92 95% CI, 1.29 – 2.86).[421] For the three case–control studies, the overall association between Agent Orange exposure and spina bifida was statistically significant (Summary Odds Ratio = 2.25, 95% CI, 1.31 – 3.86). The cross sectional study also showed a statistically significant association (RR = 1.97, 95% CI, 1.31 – 2.96), but the three cohort studies did not (RR: 2.11, 95% CI, 0.78 – 5.73). Ngo and colleagues concluded that paternal exposure to Agent Orange appears to be associated with a statistically increased risk of spina bifida.[421]

4.0 Comparing Historical and Recent Information

The reports on the human volunteer trials published by the National Academies of Science in the 1980s provided a tremendous amount of information about these tests to the public for the first time. They remain important historical documents because of so much of the original documentation on the trials has been fragmented or lost over time. However, some of the conclusions they came to regarding the potential for long-term sequelae as a result of exposure to the test compounds is outdated and does not agree with recent experimentation and analysis. Notable examples of this can be seen in the report's conclusions on sarin and other anticholinesterases (especially other G-Series agents); on LSD and other classical hallucinogens; and on the irritant CS (Chlorobenzylidene malononitrile), and the vesicant, sulfur mustard.

Anticholinesterases

The historical reports did not have consistent and compelling evidence for the long-term negative health effects of exposure to anticholinesterase chemicals. More recent work on the subject, including the Institute of Medicine's health analysis from 2007 concluded that two distinct long-term sequelae to organophosphate exposure exist:

- Organophosphate-induced delayed polyneuropathy (OPIDP), and,
- Chronic organophosphate-induced neuropsychiatric disorder (COPIND).

These syndromes have been vetted and embraced by both military and civilian experts, and continue to be used as perceptual frameworks about which ongoing studies are conducted.

In addition to official reports, there are now significant bodies of scientific literature on the health outcomes of Gulf War Veterans, and the health of soldiers and civilians exposed to anticholinesterases in the Iran-Iraq War and in the terror attacks by Aum Shinrikyo.

LSD & Other Hallucinogens

The reports on the human-exposure LSD trials by the Department of the Army for the Inspector General in the 1970s and those by the National Research Council in the 1980s acknowledged the existence of sometimes profound cognitive (flashbacks) and psychological sequelae (transient psychoses) associated with LSD ingestion, but noted that a very small number of volunteers had experienced any of these events.

By contrast, recent work on the long-term health of people using LSD or other classical psychedelic drugs (psilocybin, DMT, & mescaline) have found no negative health effects associated with the willing ingestion of these drugs. Many of the recent studies have been done using population-level databases with thousands of cases instead of isolated case reports of adverse

effects or sequelae. Detailed investigation of the reports of negative health effects have found that the prevalence of flashbacks has been greatly overestimated in the past. Additionally, many of the people reporting negative effects are individuals who have (sometimes serious) pre-existing psychiatric conditions prior to hallucinogen use, or are people who habitually mixing drugs from different classes.

CS (Chlorobenzylidene malononitrile) & Sulfur Mustard

The National Academies reports described some of the volunteers has having allergic contact dermatitis after exposure to the irritant CS, and skin lesions after dermal application of sulfur mustard. However, they interpreted the effects of exposure to both of these compounds as transient, or resolving in a few weeks after exposure, instead of as a long-lasting negative health impact.

Recent clinical reports by Barghava, and Watson have shown allergic contact dermatitis and other cutaneous conditions that have arisen from CS exposure to be long lasting, or even a life-long condition.[95,96] Likewise, recent documentation of the cutaneous lesions from sulfur mustard in Iranian veterans has shown that some sequelae can persist for years.

The difference in the disparities in these two cases is probably dose-dependent, with the larger doses (in-theatre offensive use of) or more frequent doses (training for CS use) producing the longer-term sequelae, than the smaller doses used on the soldiers in the volunteer studies.

5.0 Conclusions

Of the more than 100 agents and compounds researched for this study, 18 had evidence for potential long-term sequelae associated with exposure. There were 16 different types of sequelae that ranged from neurological disorders to carcinomas. The most frequently seen sequelae were neurological, which occurred in 7 of the 18 compounds. The next most common types of sequelae were cognitive, cardiac, and cutaneous which were each noted in 5 compounds. A higher risk of sarcomas or carcinomas was noted in those exposed to 4 substances. Some types of sequelae were noted only in association with one compound, as in the case of movement disorders (dystonias and dyskinesias) and butyrophenone derivatives.

Table 18. Strength of Association Between Compound Exposure and Sequelae

Agent or Compound	Low	Medium	High
C. burnetii			X
EEE/WEE/VEE			X
C. botulinum			X
Tabun			X
Sarin			X
Soman		X	
DFP			X
Malathion			X
Lysergamides	X		
CS	X		
Butyrophenone derivatives	X		
Sulfur Mustard			X
Phosgene			X
Dioxins			X
Arsenic			X
Chloramphenicol	X		
Tetracycline	X		
PABA		X	

The associations between exposures and sequelae varied in strength from weak – like the association between aplastic anemia and chloramphenicol use – to strong – like the association between neurological abnormalities in survivors of infection from the equine encephalitis viruses (See Table 18.) Eleven of the 18 compounds had strong associations between agent exposure and possible long-term sequelae. Five agents had weak associations between exposures and sequelae and two agents had medium associations

A strong association could be made because the condition was well documented by a number of authors in different populations over time, or because the association was based on a large population study or a high-quality meta-analysis.

Similarly, a weak association was based either on an extremely low population prevalence, like the hematological problems associated with chloramphenicol, or by uncertainty in which exact drug from a large class was tested on volunteers as in the case with lysergamides or the butyrophenone derivatives. CS had a weak association because although sequelae have been documented several times,

Table 1. Potential Long-Term Sequelae from Exposure to Agents or Compounds in this Study

Agent or Compound	Neurological	Cognitive or Learning	Depression	Fatigue	Psychosocial	Anxiety	Cardiac or Vascular	Muscle Weakness	Movement	Respiratory	Neuroendocrine	Bowel	Cutaneous or Allergic	Ocular	Blood or Marrow	Cancer
C. burnetii	X			X			X									
EEE/WEE/VEE	X															
C. botulinum	X			X				X								
Tabun	X	X						X								
Sarin	X	X				X	X			X	X					
Soman						X										
DFP	X	X														
Malathion		X	X													X
Lysergamides					X		X									
CS													X			
Butyrophenone derivatives							X		X							
Sulfur Mustard	X	X			X	X				X			X	X		X
Phosgene										X						
Dioxins	X												X			X
Arsenic							X						X			X
Chloramphenicol															X	
Tetracycline												X				
PABA													X			

most reports are of individual cases or come from studies with methodological problems, such as failure to perform adequate sensitivity analyses to rule out confounding factors. When well-controlled for, however, sometimes factors that exist before exposure can be somewhat predictive of adverse effects or sequelae, as when heavy smokers or people with asthma or other lung diseases are exposed to irritant gasses.

Sequelae by Compound or Substance

The anticholinesterases had the largest number of sequelae associated, with five out of 10 compounds associated with the long-term negative effects of exposure. By comparison, only three of 15 biological agents or vaccines had information about related sequelae in the recent scientific or medical literature.

Sulfur mustard had the largest number of sequelae associated with it, and these ranged from respiratory problems to psychosocial and cognitive issues. Some compounds, on the other hand, were outdated or experimental and obscure and little or no information could be found about their long-term adverse effects. To some degree also, estimations of, "the most" or "the least" sequelae have a certain amount of study bias associated with them.

Neurological Sequelae

Looking more closely at neurological sequelae, we can see that the most common manifestation is seen as a motor or movement sequelae such as in a psychomotor impairment with EEE/WEE/VEE infection or problems balancing or walking without falling over as is sometimes seen as a long-term consequence of sarin exposure. (See Table 19.)

Table 19. Neurological Sequelae by Agent or Compound

Agent or Compound	Coma	Seizures	Motor or Movement	Speech or Comprehension	Depression	GNS Neuropathy	Peripheral Neuropathy	Weakness & Fatigue	Sensory
C. burnetii						X	X		
EEE/WEE/VEE	X	X	X	X	X				
C. botulinum			X		X			X	
Tabun			X					X	X
Sarin			X			X			
DFP			X						
Sulfur Mustard		X			X		X	X	X
Dioxins							X		X

EEE/WEE/VEE infection had the broadest range of neurological sequelae associated with it, ranging from patients presenting with persistent seizures to those who had difficulty with speech or comprehension. Some 40 percent of people who survive severe Q-Fever infection in some populations can develop central nervous system or autonomic neuropathy; peripheral polyneuropathies may also occur, although they have been documented in less than 5 percent of survivors. Weakness and fatigue also occur as sequelae after infection with *C. botulinum*, or after exposure to tabun or sulfur mustard.

Balali-Mood found that almost 80 percent of Iranian veterans recovering from sulfur mustard exposure and signs of peripheral polyneuropathy and that this was confirmed by abnormal neural conduction tests.[106] A similar polyneuropathy was also seen more than thirty years after an industrial accident with dioxin, indicating the long-term nature of some sequelae.[138]

Table 20. Cognitive Sequelae by Agent or Compound

Agent or Compound	Learning	Memory	Visual Attention	Perception	Abstraction	Problem-Solving	Dexterity
Tabun	X	X					
Sarin		X	X				
DFP	X	X	X		X	X	X
Malathion	X	X	X	X			
Sulfur Mustard		X					

Cognitive Sequelae

Turning now to cognitive sequelae, we see that DFP has the broadest range of cognitive symptoms associated with it. (See Table 20.) These range from learning and deficits to problem solving and dexterity issues. It is important to note that there is disagreement in animal studies about the persistence of these sequelae. Some studies show most deficits correcting themselves in the months after DFP dosing has ceased, and others do not.

Malathion exposure is also related to a similar range of sequelae. People with chronic high exposure (> 10 years) as well as those with acute poisoning had significantly lower scores on verbal memory, perceptive learning, and attention tests than did matched control subjects.

Anticholinesterase chemical warfare agents are also associated with cognitive sequelae. From follow-up on survivors of the Aum Shinrikyo attacks, we know that sarin is associated with mild memory loss. An observation that is supported by water-maze tests with rodents, who demonstrated problems in visual-spatial memory tasks after tabun exposure.

Long-term follow-up on Iranian survivor of sulfur mustard attack also show high levels cognitive and memory-related sequelae (> 70%). However, like the studies on the Tokyo-subway attack victims, these follow-up studies do not control for confounding factors like PTSD that may also affect cognition.

Cardiac and Vascular Sequelae

Five agents or compounds were also associated with cardiac or vascular sequelae: *C. burnetii*, sarin, lysergamides, butyrophenone derivatives, and arsenic. (See Table 21.) The most commonly seen sequelae was one of vascular stenosis or insufficiency, which was found associated with Q-fever, and exposure to lysergamides or arsenic. In the case of Q-fever, a recent population study from the Netherlands has found slightly more than 30 percent of cardiac patients with aortic or iliac disease to be positive for *C. burnetii* infection. This is a much greater than expected association, as most previous studies indicated the potential for vascular insufficiency to be under 10 percent of those infected.

Table 21. Cardiac or Vascular Sequelae by Agent or Compound

Agent or Compound	Endocarditis	Vascular Infection	Vascular Insufficiency	Cardiac Conduction	Cardiac Valves	Arrhythmias	Cardiac Remodeling & Performance	Myocardial Infarction	Aneurysm	Sudden Cardiac Death
C. burnetii	X	X	X		X				X	
Sarin						X	X			
Lysergamides			X		X			X		
Butyrophenone derivatives				X						X
Arsenic			X	X		X		X		

Valvular patency or problems with regurgitation are associated with infections with *C. burnetii* as are vascular infections and endocarditis. Cardiac valve problems are also noted in some patients taking lysergamides.

Cardiac conduction problems, such as prolonged QT-intervals are associated with arsenic exposure and ingestion of haloperidol, a butyrophenone derivative incapacitant.

In animal studies with mice, sarin-treated animals demonstrate high levels of cardiac remodeling that decreases heart performance. This remodeling can either affect whole heart weight relative to body size, or just the ventricular lumen. It is not clear what mechanisms underlie these changes, but autonomic neuropathy is believed to play an important role.

Cutaneous Sequelae

Sulfur mustard exposure can produce a broad range of skin sequelae ranging from severely dry and itchy skin with or without areas of hyper- and hypo pigmentation, which develop into seborrheic dermatitis or chronic eczema. (See Table 22.) Spider veins – which can be mild or disfiguring – are also common in victims of sulfur mustard attacks.

Table 22. Potential Cutaneous Sequelae by Agent or Compound

Agent or Compound	Dry Skin (Itching, peeling)	Allergic Contact Dermatitis	Seborrheic Dermatitis	Chronic Eczema	Hyper- or Hypo-pigmentation	Spider Veins	Dyses-thesia	Chlor-acne	Hyper-keratosis	Bowen's Disease
CS		X	X		X		X			
Sulfur Mustard	X		X	X	X	X				
Dioxins								X		
Arsenic					X				X	X
PABA		X		X						

Allergic contact dermatitis sometimes occurs with exposure to the irritant CS and the sunscreen ingredient PABA. Painful, red plaques can develop in the exposed area that can last for months after exposure. There are also documented cases that appear to be permanent. These cases may require changes in lifestyle – especially if exposure was occupational as is the case with some law-enforcement officers training to use CS.

Chloracne, a chronic inflammatory skin condition characterized by keratinous plugs with cysts and dark acne caused by problems in liver function is a characteristic cutaneous sequelae of dioxin exposure. A high-profile case occurred in 2004 when former Ukrainian President Viktor Yushchenko ingested a large dose of dioxin. Liver and pancreas dysfunction eventually led to chloracne which left him disfigured for many years after the event.

Arsenic exposure also produces a characteristic nodular hyperkeratosis on the palms and soles of the feet. These areas of thickened epidermis can be interspersed with areas of hyper- and hypopigmentation and sometimes form, "raindrop," patterns. These early changes in the skin associated with arsenic also predispose to the development of a variety of skin cancers, and a squamous cell carcinoma (*in situ*) known as Bowen's Disease may also develop. After a latency period that can last years, or even decades, non-melanoma skin cancers, including frank squamous-cell carcinomas and basal-cell carcinomas can also develop.

Cancer

In addition to being associated with cutaneous cancers, arsenic exposure has also been linked to gastrointestinal and lung cancers as well. (See Table 23.) A study done in the in the Antofagasta area of Northern Chile, where arsenic levels were as high as 800 – 900 mg/L between the late 1950s and the mid- 1970s, but lower thereafter found an exposure-level related relationship between the risk of lung cancer (OR) and arsenic exposure. The ORs were 1.00 for < 11 mg/L (reference), 1.27 (95% CI, 0.81–1.98) for 11-90 mg/L, 2,00 (1.24–3.24) for 91-335 mg/L, and 4.32 (2.60 – 7.17) for >335 mg/L.

Table 23. Potential Cancers Associated with Exposure to Agents or Compounds

Agent or Compound	Testicular Cancer	Lymphatic	Hematological	Gastrointestinal	Visceral Sarcomas	Soft-tissue Sarcomas	Cutaneous	Lung
Malathion	X							
Sulfur Mustard		X	X	X				
Dioxins					X	X		
Arsenic				X			X	X

A study in Venice correlated dioxin exposure with cancers in the tumor registry and found that the risk of developing a visceral or extra-visceral sarcoma was 3.3 times higher (95% CI: 1.24 – 8.76) among people with the longest dioxin exposure at the highest exposure level.

Using the nearly 100,000 individuals registered in the Agricultural Health Study (AHS) database, as recent prospective cohort study found a correlation between chronic Malathion exposure and aggressive prostate cancer (RR = 1.43) for the highest quartile of exposure vs. nonexposed.

Discussion

This literature review, which looked for associations between more than 100 biological or chemical warfare agents, industrial pollutants and miscellaneous drugs and compounds, found evidence that some of these substances (18/93) are sometimes associated with long-term sequelae that negatively impacts their health or the quality of life. That said, it is important to remember that this information gathered for this analysis was recently published (6/30/2006 – 12/1/2015) and most of it was unknown to the soldiers and civilians who administered the volunteer human exposure tests which took place from the 1950s to the 1970s.

The records of the tests published by the National Academies of Science in the 1980s showed that the volunteers were carefully screened prior to the tests; exposures were low relative to

many of the sequelae-inducing doses in the recent literature; and the tests were terminated immediately if the volunteers experienced moderate-to-severe discomfort. Additionally, the health impact of volunteers was assessed at several different time periods in the years following their exposures, and no significant sequelae were recorded in any of the follow-up health screenings.

Furthermore, a great deal of the recent public health and medical literature consulted for this study involves sequelae that may arise for long-term exposures or chronic use of a medication or substance. By contrast, the volunteer tests consisted of a single exposure or on occasion, a short series of exposures

Additionally, some of the information presented in this report about associated sequelae comes from animal studies. This information is informative, but should not be taken as indicative of the sequelae that might occur following human exposure to these compounds. Rather the animal experiments should be regarded as, "proof of concept," of sequelae that might arise in humans after exposure, or supportive of human epidemiological and medical data, if available.

Lastly, there are some discrepancies between the historical analyses of health outcomes from the human exposure trials performed by the National Research Council panel in the 1980s, with the Institute of Medicine's review published in 2007 and some of the literature reviewed for this report. These differences have arisen as consequences of our improved medical and scientific understanding of these compounds and conditions, not because of any attempt to deny or hide the negative health impacts associated with exposure.

Appendix 1: Agents, Compounds and Substances

Biological Agents

Coxiella Burnetii (Q-fever)

Q-fever is a disease caused by infection with the intracellular bacterium *Coxiella burnetii*. The most common symptoms of infection are mild flu-like symptoms with abrupt onset of fever, malaise, profuse perspiration, severe headache, myalgia, and joint pain, loss of appetite, upper respiratory problems and gastrointestinal symptoms.

Figure A-2. C. burnetii inside replication vacuole. (Credit: Beth Fisher, Rocky Mountain Laboratory)

On occasion, acute Q-fever can progress to an atypical pneumonia, which can be severe if left untreated. Less often, Q-fever causes granulomatous hepatitis, which presents as malaise, fever, hepatomegaly, and pain in the upper abdomen. A common symptom of chronic Q-fever is endocarditis, which can occur months or years after infection, and can be fatal if untreated. It can also be treated as a long-term sequelae of Q-fever because it can emerge long after the original infection, and persist after the recurring infection has been eradicated.

Naturally occurring Q-fever is a zoonotic disease and human cases usually result from contact with infected animals or improperly disposed tissue and fluids from infected animals. Ticks can also be a vector for the spread of the bacterium. Infective dose is very low for all animals, and has been determined to be 18 $MICLD_{50}$/person (mouse intracerebral units) in human tests. The incubation period ranges from 9 to 40 days, but usually last for two to three weeks. Approximately half of infected individuals exhibit no symptoms.

Francisella tularensis (Tularemia)

There are multiple subspecies or biovars of the pathogenic bacterial species *F. tularensis* that cause disease of varying symptoms and severity. The subspecies *F. tularensis* (Type A), however, causes the most severe type of disease, and is the focus of this report.

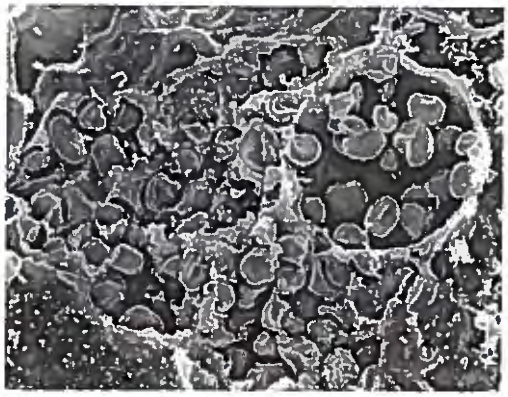


Figure A-2. F. tularensis bacteria. (Credit: NIAID)

Within the *tularensis* biovar, symptoms of natural tularemia infection range from cutaneous sores to severe atypical pneumonia, depending upon the route of infection. Other routes of inoculation have been described and include oropharyngeal or gastrointestinal infection due to consumption of contaminated food and conjunctival infection due to inoculation at the eye.

In the environment, *F. tularensis* is capable of surviving outside of a mammalian host for long periods of time and has been found in water, grassland, and haystacks. It also has an extremely low infectious dose and easily becomes airborne in primary and secondary aerosols. Like *Yersinia* species, it reproduces preferentially within macrophages, first suppressing the cells ability to destroy them after phagocytosis and then facilitating cell death to escape and proliferate infection.

Plasmodium vivax (Vivax Malaria)

Plasmodium vivax is a protozoal parasite and the cause of vivax malaria. Vivax malaria is traditionally thought to be less acute than malaria caused by *Plasmodium falciparum*. However, a recent surge in studies from Latin America and Asia documenting severe symptoms and sequelae resulting from *Plasmodium vivax* infection has prompted a reassessment of its impact. A meta-analysis comparing the incidence of severe malaria, severe anemia and mortality between *P. vivax* and *P. falciparum* mono-infection published in 2014 found the prevalence of severe malaria comparable in infants, children under five-years of age, children ages five to 15 years, and adults.

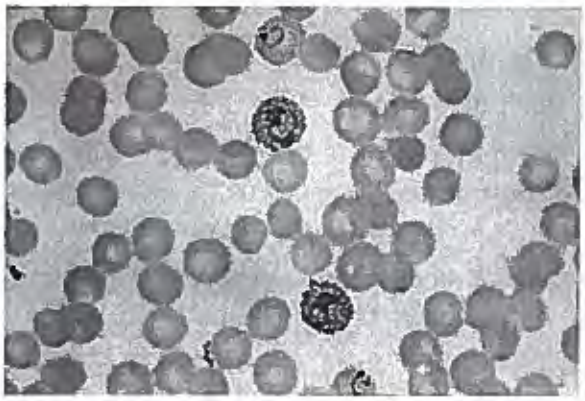


Figure A-3. Plasmodium vivax, trophozoite stage. (Credit: Steven Glenn, CDC)

The incidence of severe anemia was also comparable in infants, and in children ages five to 15 between the groups. Mortality was lower in infants, but comparable in children ages five to 15. Clearly, *P. vivax* malaria is not a benign as once thought.

Still, separating symptoms from long-term health effects or sequelae is difficult with vivax malaria, largely because of periods of latency and dormancy that can last from days to years. During these periods, the parasites sequester within hepatocytes as hypnozoites, and cause no

symptoms. They are also undetectable in blood tests at this time. Thus, a single infectious bite can trigger multiple relapses of disease and leave the host more vulnerable to other infectious and chronic diseases. Likewise, infection with other diseases or conditions can trigger relapses of vivax malaria.

Staphylococcal Enterotoxin B (SEB)

Staphylococcal enterotoxin B (SEB) is a toxin produced by the bacterium *Staphylococcus aureus*. The function of the toxin is to facilitate the infection of the host organism and induce pathogenesis.

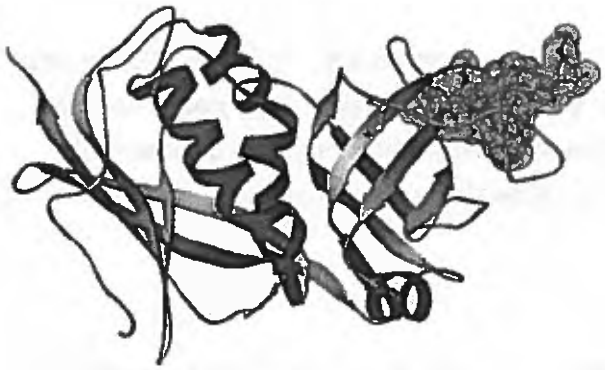


Figure A-4. Staphylococcus enterotoxin B (SEB). Credit: S. Swaminathan, Brookhaven Nat'l Lab

In nature, *S. aureus* toxins are a common cause of food poisoning, with severe diarrhea, nausea, and cramping starting within a few hours of ingestion. SEB is very stable, and may remain active long after the contaminating bacteria are killed. It can also withstand temperatures above 100 degrees centigrade for several minutes without degrading. Gastroenteritis occurs because SEB is a superantigen, and it causes the immune system to release a large amount of cytokines (activation of a significant fraction of T-cells (up to 20%)) that lead to significant inflammation.

In addition to gastroenteritis from ingestion of the toxin, fever along with gastrointestinal and pulmonary symptoms can result from inhalation, and conjunctivitis and local facial swelling can result from ocular and cutaneous exposure. Additionally, severe intoxication can result in rapid pulmonary edema, adult respiratory distress syndrome, shock, or death. The time from exposure to illness, and the severity of symptoms is dose dependent. In humans, the estimated LD_{50} is 0.02 µg/kg and the ED_{50} is 0.0004 µg/kg by aerosol route.

Pseudomonas Endotoxin

The lipopolysaccharide (LPS) component of *Pseudomonas aeruginosa* is a major part of its outer membrane – a characteristic shared with other gram-negative bacteria. The LPS contributes greatly to the structural integrity of the bacteria, and protects the membrane from chemical attack. It is also an endotoxin that induces a strong response from normal animal immune systems. It has been implicated in non-pathogenic aspects of bacterial ecology, including surface adhesion, bacteriophage sensitivity, and interactions with predators such as amoebae.

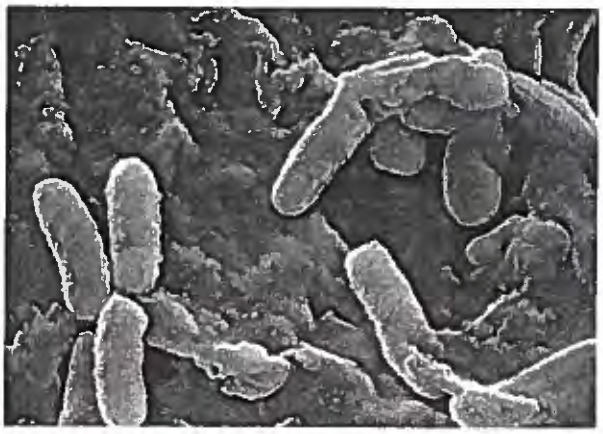


Figure A-5. Pseudomonas aeruginosa micrograph. (Credit: Janice Haney Carr, CDC)

A growing body of experimental evidence suggests that *P. aeruginosa* LPS plays an important role in the pathophysiology of infection. Some studies show that the LPS degrades the surface of target tissues, thereby facilitating bacterial infection. In studies of LPS effect on skeletal muscles, LPS produces deleterious effects on vasomotor tone and can possibly underlie the intractable hypotension observed in patients with *P. aeruginosa* sepsis.

Moreover, *P. aeruginosa* endotoxemia, particularly of intestinal origin, is implicated in a number of diseases, including alcoholic hepatitis. Although precise mechanisms of disease pathogenesis are unknown, it is thought that bacterial overgrowth and toxin release increases intestinal permeability.

Sandfly Fever, Sicilian Strain

Sandfly fever, also known as Pappataci fever or phlebotomus fever is a disease transmitted by Phlebotominae sandflies that causes fever, myalgia, and malaise along with abnormalities in liver enzymes and hematological markers. The Mediterranean basin is the main area for sandfly fever transmission, with natural cases occurring from Spain and Morocco to Turkey and Iran. Cases have fever resulting from Sicilian Strain viruses have also recently been reported from the Afar region of Ethiopia.

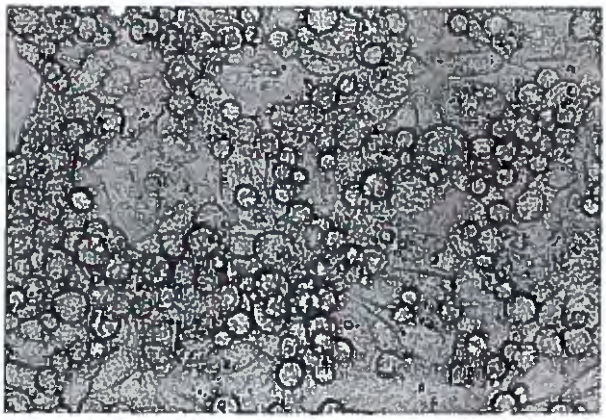


Figure A-6. Phlebovirus (Credit: CDC)

Sandfly fever viruses are classified within the Phlebovirus genus of the Bunyaviridae family, with a segmented negative-strand RNA genome. Sandfly Fever is one of ten recognized serogroups within the Phlebovirus genus, and is divided into two groups: Naples and Sicilian. Within the Sicilian group are seven viruses Belterra virus, Chagres virus, Corfu virus, Rift Valley fever virus, and the closely related Sandfly fever Cyprus, Sicilian and Turkey viruses.

Eastern, Western, and Venezuelan Equine Encephalitis

Alphaviruses are enveloped, positive-stranded RNA viruses, spread by mosquito vector, that are the etiologic agents of severe encephalitis and polyarthritis. Three of seven alphavirus serocomplexes are represented by the equine encephalitis viruses: eastern equine encephalitis (EEE), western equine encephalitis (WEE), and Venezuelan equine encephalitis (VEE). In nature, these viruses have widespread distributions in North, Central and South America, and can pose a threat to human and animal health. EEE is found along the Atlantic and Gulf coasts as well as out to the mid-West, and WEE from the mid-West to the west coast and up into Canada. By contrast, the transmission of VEEV occurs predominantly in Central and South America. Mosquito vector species vary with geographic distribution, affecting the zoonotic potential of the viruses.

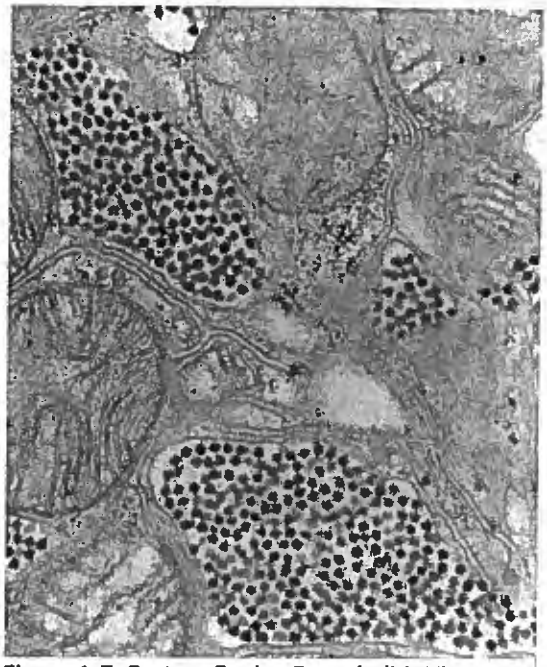


Figure A-7. Eastern Equine Encephalitis Virus (Credit: Fred Murphy; Sylvia Whitfield, CDC)

Traditionally, EEE is viewed as the most severe of the encephalitic alphaviruses with the case-fatality rate in humans estimated in the range of 50 to 70 percent. WEE is generally much less severe with an estimated case-fatality of 3 to 7 percent. This may be because of the high number of asymptomatic cases in potentially infected populations that increases from 1:1 relative to clinical cases in infants under the age of one, to >1000:1 in children over the age of 14 years. Natural human case fatality from VEE is usually 1-3 percent of those infected. VEE generally results in flu-like symptoms for humans with encephalitis being rare. It is, however, highly transmissible by aerosol route and outbreaks can be large.

Typhoid Fever

Typhoid fever is a common disease caused by the bacterium *Salmonella enterica* serovar Typhi. It is usually transmitted by the ingestion of contaminated water or food. The course of untreated typhoid fever is divided into four individual week-long stages, including fever, malaise and flu-like symptoms in week one, a prostrate fever with multi-organ dysfunction in week two, complications and spontaneous resolution in weeks three and four, respectively.

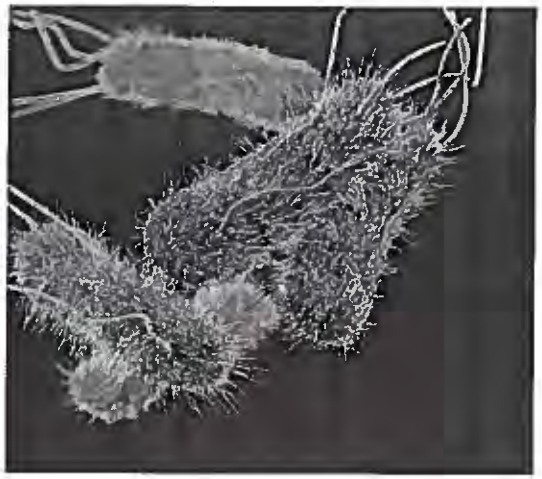


Figure A-8. Salmonella enterica, serovar Typhi (Credit: Melissa Brower, CDC)

Prior to the widespread use of antimicrobial medications, typhoid fever had a case-fatality rate of 10-20 percent. With improved sanitation, agricultural hygiene, and the use of antimicrobials, mortality from disease fell significantly to near one percent. However, in the past several decades emergence and rapid spread of drug-resistant strains are causing disease severity and mortality to rise once again, especially in the developing world.

Rickettsia rickettsii (Rocky Mountain Spotted-Fever)

Rocky Mountain spotted fever (RMSF) is the most frequently reported rickettsial illness in the United States, with approximately 1200 cases presenting annually. The disease is caused by *Rickettsia rickettsii*, an intracellular bacterium that is spread to humans by ticks of the genera *Dermacentor*, *Rhipicephalus*, or *Amblyomma*.

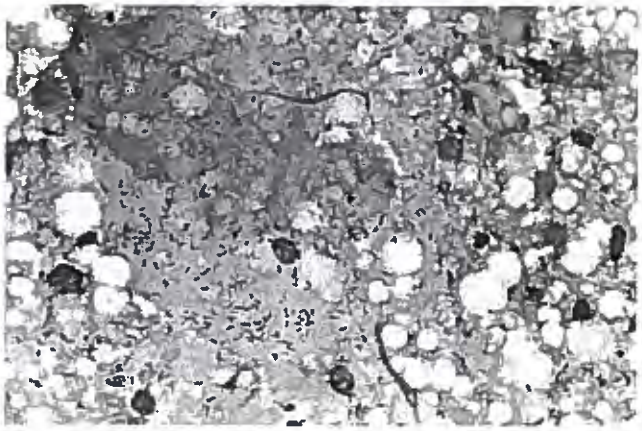


Figure A-9. Rocky Mountain Spotted Fever Virus (Credit: Billie Ruth Bird, CDC)

The name Rocky Mountain spotted fever is somewhat of a misnomer, because RMSF cases have been reported from all states within the continental U.S. It is also reported from Mexico, Central and South America, and Canada. Approximately 90 percent of all infections occur within the months of April to September, when populations of adult and nymphal ticks are the highest.

Initial signs and symptoms of the disease include sudden onset of fever, headache, and muscle pain, followed by the development of the characteristic rash. The disease can be difficult to diagnose in the early stages, and without prompt and appropriate treatment it can be fatal. Prior to the use of antimicrobial medications to treat RMSF, case fatality was a high as thirty percent. Now, however, treatment has caused mortality to fall to three to five percent.

Clostridium botulinum (Botulism)

Botulism is a rare and potentially fatal paralytic illness caused by a toxin produced by the bacteria *Clostridium botulinum*. It usually occurs when spores are ingested or toxin inhaled, but in recent years, there have been many cases of cutaneous origin in injecting-drug users. Typical symptoms of botulism include lethargy and progressive weakness, drooping eyelids or facial muscles, and difficulty speaking or breathing, progressing to a complete descending flaccid paralysis. Botulinum toxins are subdivided into eight neurotoxins: Types A through H, which are antigenically and serologically distinct but structurally similar. Botulism in adults is usually caused by toxin types A, B, E, although rare cases of intoxication with types F and G have been reported.

Figure A-10. Clostridium botulinum (Credit: Dr. Holdeman, CDC)

The growth and lysis of *Clostridium botulinum* spores releases botulinum toxin, which is then absorbed into the bloodstream and taken throughout the body, causing paralysis by blocking the release of acetylcholine at the neuromuscular junction. Treatment is with appropriate antitoxin and is most effective if delivered quickly, before toxin has bound at the receptor sites.

Case fatality rates in the U.S. from natural disease are between 3 and 10 percent, but can be much higher in older adults. Historically, mortality was much higher at 60 to 70 percent, but fell precipitously with the use of mechanical ventilation and improved supportive care. Patients with severe botulism may require ventilation and intensive care, sometimes for several months.

Organophosphorus Nerve Agents

The organophosphorus (OP) nerve agents belong to a chemically diverse group of organic compounds that have in common at least one carbon atom bound to a phosphorous atom. They are sometimes referred to as nerve gases because of the high volatility of some of the specific agents, but in fact, they are clear, colorless liquids at room temperature. The OP nerve agents were derived from OP pesticides during World War II by the Nazis to be used as chemical warfare agents (CWAs). Traditional OP nerve agents fall into two groups, the G- and the V-series, based on their chemical and physical properties.

The G-series nerve agents [tabun (GA); sarin (GB); and Soman (GD)] are volatile liquids at room temperature that can be deadly when inhaled as a vapor or from percutaneous exposure to the vapor. V-series agents (VX and others) have a consistency similar to oil and do not evaporate rapidly. The V-series agents can remain on clothing and other surfaces for a long time, and they pose a greater risk from dermal exposure or by ingestion. Agents in the V-series are approximately 10- to 100-fold more toxic than those in the G-series.

OP nerve agents inhibit the catalytic function of acetylcholinesterase (AChE).[422] This removes the capacity of the enzyme to catalyze acetylcholine (ACh). As a consequence, the hydrolysis of ACh is prevented, leading to accumulation of ACh in the synaptic cleft and overstimulation and subsequent desensitization of ACh receptors at cholinergic synapses in the brain, glands, and skeletal and smooth muscles.
(See Figure 1.)

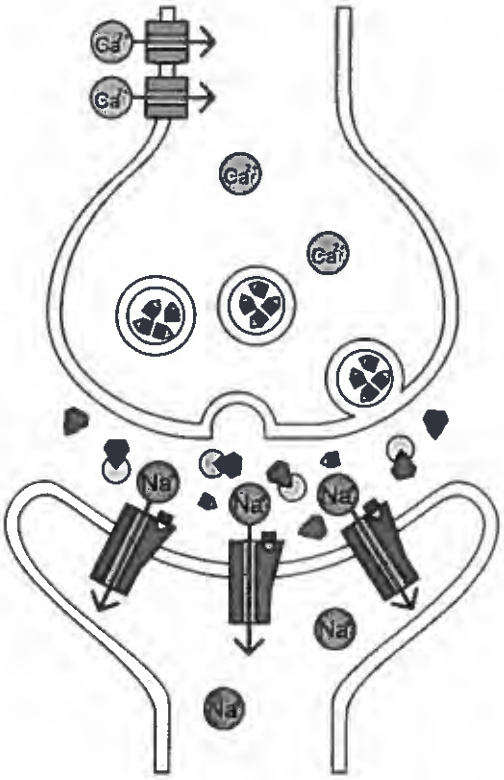


Figure A-11. The Biological effects of Organophosphate (OP) Compounds at the Neuromuscular Junction. OP Compound (red), Acetylcholinesterase (yellow), Acetylcholine (blue). (Note the build-up of acetylcholine in the junction which leads to constant firing of the effected nerve.)

The acute effects of OP nerve agents and pesticides include a progression from lack of response to light, excessive secretions, and muscle fasciculation to epileptic seizures, muscle paralysis, cardiorespiratory depression, and death by respiratory failure. If the subject survives the first day of poisoning, personality changes, mood swings, aggressive events, and psychotic episodes including schizoid reactions, paranoid delusions, and exacerbations of preexisting psychiatric problems may also ensue. Sleep quality is disturbed due to the occurrence of nightmares and hallucinations, disturbances or deficits in memory and attention, as well as additional delayed effects.[423,424]

Tabun (GA, EA 1205)

Originally developed as an insecticide in 1936, tabun (O-ethyl-N,N-dimethyl phosphoramidocyanidate) is a highly toxic organophosphorus compound that may also be used as chemical warfare agent. It was the first of the G-Series agents to be developed, and in the Second World War, Germany produced over 12,000 metric tons of it before the manufacturing plant was shut down by allied forces.

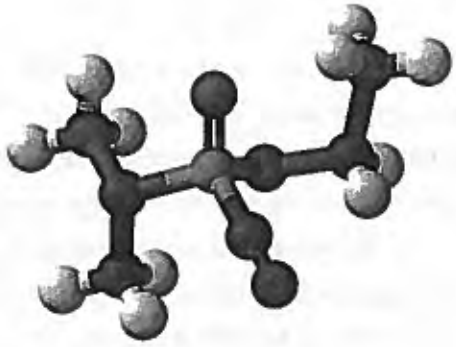


Figure A-12. The Chemical Structure of Tabun. Credit: Amir Ahrls, 2012

Exposure can be through inhalation, contact with the skin, eyes, or mucus membranes, or ingested in contaminated food or water. Tabun is a compound of moderate volatility, which means that it can remain toxic on environmental surfaces or substances for minutes to hours. Additionally, tabun breaks down slowly once ingested or absorbed, allowing it to build up in the body with repeated exposures. It also differs from other OPs in that many commonly used antidotes are not able adequately to prevent tabun-induced acute toxic effects, such as central-nervous system mediated seizure activity, which can lead to profound long-term disability after exposure.

Sarin (GB, EA-1208)

Sarin was discovered in 1938, and like tabun, the finding was made by German scientists attempting to create stronger pesticides for the IG Farben Corporation. It was found to be many times more toxic than tabun, and it was slated for use in WWII within a year of its discovery. Sarin, named in honor of its discoverers, Schrader, Ambros, Ritter, and Van der Linde, was produced and loaded into artillery shells, but never used against allied forces.

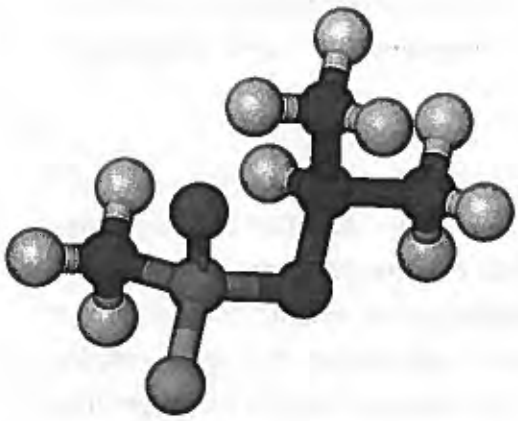


Figure A-13. Chemical Structure of Sarin Credit: Amir Ahrls, 2012

Since then, sarin has been used as a weapon on both military and civilian populations by state actors. Iraqi forces used sarin in attacks against Iranian soldiers near the end of the Iran-Iraq War in the 1980s. Around the same time, in 1988, the Iraqi government also used it against its Kurdish population, killing 5,000 people and injuring many more. More recently, in 2004, Iraqi insurgents attempted to detonate a shell containing precursor chemicals for sarin near U.S. forces. The shell, however, did not detonate correctly, and only two servicemen showed symptoms of exposure. In 2013 the Syrian government used sarin against the rebels in Syria's civil war.

Sarin has also been used in terrorist attacks by the Aum Shinrikyo cult in attacks on civilian populations in Japan in 1994 (Matsumoto attack) and 1995 (Tokyo subway attack). Those two attacks combined, killed 21 people, exposed more than 5,000 people to sarin, and injured hundreds.

Soman (GD, EA 1210)

Soman, or GD (O-Pinacolyl methyl-phosphonofluoridate), is a volatile, corrosive, and colorless liquid that was the third of the G-series nerve agents to be invented along with tabun (GA), sarin (GB), and cyclosarin (GF). Like many other nerve agents, soman interferes with normal functioning of the mammalian nervous system by inhibiting acetylcholinesterase. Soman is more lethal and more persistent than sarin or tabun, but less so than cyclosarin.

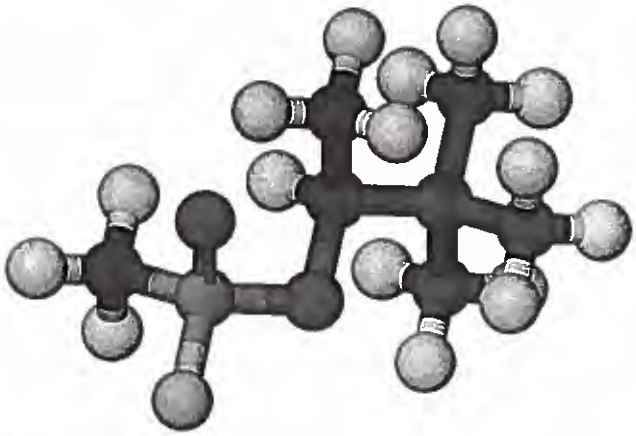


Figure A-14. Chemical Structure of Soman. Credit: Amir Arhls, 2012

The LCt_{50} for soman is estimated to be 70 mg·min/m^3 for humans, a value that is a fraction of the LCt_{50} for rodents (954.3 mg·min/m^3). It can be used as a binary chemical weapon, or it can be thickened for use as a chemical spray using an acryloid copolymer. It is extremely toxic by all routes: inhalation, contact, and ingestion, with exposure to a 1% LCt_{50} dose causing miosis in some individuals.

Regardless of the route of exposure, the initial manifestations of soman toxicity includes runny nose, chest tightness, pinpoint pupils, shortness of breath, excessive salivation and sweating, nausea, vomiting, abdominal cramps, involuntary defecation and urination, muscle twitching. These symptoms are followed by confusion, seizures, paralysis, coma, and in fatal cases, respiratory paralysis, and death may occur within 1 to 10 minutes, depending on the dose. Fatigue, irritability, nervousness, and memory defects may persist for weeks or months (or longer in severe cases of intoxication) after recovery from an exposure episode.

Cyclosarin (GF, EA 1212)

Cyclosarin or GF (cyclohexyl methylphosphonofluoridate) is the most toxic member of the G-series family of nerve agents by dose. Discovered in Germany, during the 1930s, cyclosarin was studied extensively by the allies after WWII. To date, however, Iraq is the only nation known to have manufactured significant quantities of cyclosarin for use as a chemical warfare agent. The Iraqi government is believed to have deployed it in battle during the Iran–Iraq war (1980–1988), often using it together with sarin.

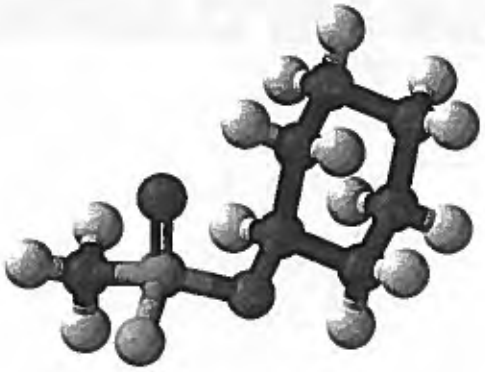


Figure A-15. Chemical Structure of Cyclosarin

At room temperature, cyclosarin is a colorless liquid, but unlike sarin, cyclosarin is a persistent liquid, meaning that it has a low vapor pressure and therefore evaporates slowly, allowing it to remain toxic in the environment longer than other G-series agents.

Sarin has a median lethal dose (LD_{50}) of 5 mg for a 70 kg human, while cyclosarin has an LD_{50} of 1.2 mg for the same size person. The median lethal concentration per unit time (LCt_{50}) of cyclosarin is 50 mg·min/m^3, which is half that of sarin.

GV (GP, EA 5365)

GV (2-(Dimethylamino)ethyl N,N-dimethylphosphoramidofluoridate) is an organophosphate nerve agent that is a part of a new series of nerve agents with properties of both the G-series- and V-series- agents. It is a potent acetylcholinesterase inhibitor similar to the Novichok (новичок) or "newcomer" series of agents developed in Russia in the 1970s and 1980s. The volatility of GV compounds is between that of sarin and VX. Therefore, these agents are effective when penetrating through uniforms and clothing and can be absorbed into porous surfaces for dispersal. GV compounds are not included in the Chemical Weapons Convention schedules of compounds. Symptoms of acute intoxication begin with agitation, followed by increased salivation, rumination and bristling. If doses are high enough, tachypnea (rapid breathing) followed by convulsions and death will follow. The LD_{50} values in rats and mice by route of administration are given in Table A-1.[425]

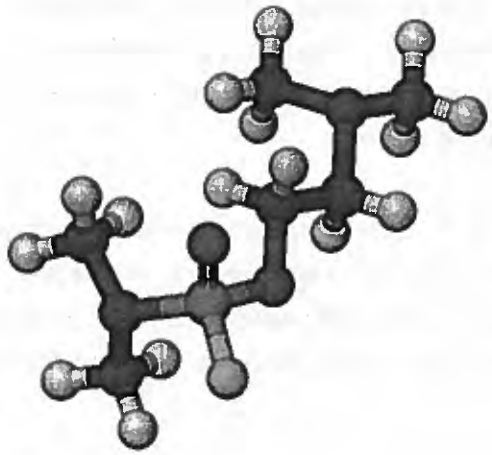


Figure A-16. Chemical Structure of GV. Credit: Amir Ahrls

Table A-1: LD_{50} Values of GV in Rats and Mice by Routes of Administration		
Route of administration	**LD_{50} (µg/kg) with their 95 % confidence limits**	
	Rats	**Mice**
Intravenous	27.6 (25.6-29.4)	11 (8.5-17.6)
Intramuscular	30.5 (28-55)	17 (15.5-23.6)
Subcutaneous	32 (29-53)	21 (18-26)
Oral (po)	.222 (194-255)	190 (881-272)
After meals (pc)	not tested	1366 (881-3138)

VX (EA 1701)

VX, or O-ethyl S-[2-(diisopropylamino)ethyl] methylphosphonothioate — is an extremely toxic substance that is a traditional chemical warfare nerve agent. It is a tasteless, odorless liquid and is the oldest of the V-series agents. It was invented in the 1950s by a British chemist (Ranajit Ghosh) investigating organophosphate pesticides and initially marketed under the trade name *Amiton*. Its use as a commercial product, however, was short lived, and it was soon withdrawn because it was too toxic for safe use. Unlike traditional CWAs in the G-series, VX is oily rather than of watery and thus evaporates so slowly that it remains an environmental hazard much longer than other OP nerve agents.[426]

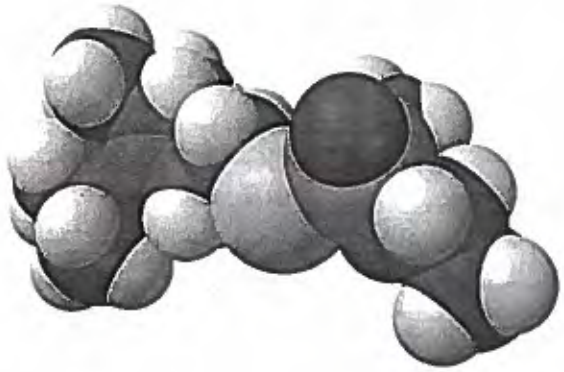


Figure A-17. Space-Filling Model of VX. Credit: Ben Mills

VX can be disseminated as a liquid, thickened with a polymer, or as an aerosol. It is toxic by multiple routes: inhaled, contact, or ingested. It is the most potent of the traditional CWAs, with the median lethal dose for humans estimated to be about 10 milligrams through skin contact, and the LCt_{50} for inhalation is estimated to be 30–50 mg·min/m^3.

Iraq claimed to have researched VX, but that they had failed to weaponize the agent due to production failures. After U.S. and allied forces invaded Iraq, however, The United Nations Special Commission (UNSCOM) laboratories detected traces of VX on Iraqi warhead remnants,[427] so it is possible that Iraq may have field-tested the agent. Aum Shinrikyo also synthesized 100 to 200 grams of VX which was used in assassination attacks against three persons suspected of spying on the cult. One of the targeted men was killed and the two others injured.

Other V-agents (VE, VG, VM)

The V-series agents are part of the group of persistent agents, which are nerve agents that can remain on skin, clothes, and other surfaces for long periods of time due to low volatility characteristics. Like VX, the consistency of these related agents is similar to oil, making the inhalation hazard low. (See Table A-2.)

The only member of the V-series (other than VX) for which historical information exists is V-Gas, also denoted VR. This agent was developed in Russia in the 1950s and 1960s. In 1972, mass production of VR began, with the Soviets making more than 15,000 tons of VR before abandoning manufacturing. Most if not all of this is believed to have been destroyed under disarmament treaties.

VR has similar lethal dose levels to VX (between 10–50 mg) and has similar symptoms and method of action as other nerve agents that act on cholinesterase and treatment remains the same. However, the window for effectively treating second generation V series seizures is shorter, as they rapidly denature the acetylcholinesterase protein in a similar manner to soman.

Treatment with the standard nerve gas antidotes are thus challenging unless delivered immediately after exposure.

Table A-2. Other V-Agents

Code Name	Chemical Name
VX	O-Ethyl-S-[2(diisopropylamino)ethyl] methylphosphonothioate
VE	O-Ethyl-S-[2-(diethylamino)ethyl] ethylphosphonothioate
VG	O,O-Diethyl-S-[2-(diethylamino)ethyl] phosphorothioate
VM	O-Ethyl-S-[2-(diethylamino)ethyl] methylphosphonothioate
VR (V-Gas)	Russian equivalent of VX

DFP (EA 1152, Diisopropyl fluorophosphate)

Diisopropyl fluorophosphate, or DFP, was developed in Britain as a chemical warfare agent in an attempt to counter the threat of nerve agent use on the battlefield by Germany. Although DFP is a potent neurotoxin, with an LD_{50} of 1.3 mg/kg in rats, it was much less effective as a chemical weapon than the G-series agents (tabun, soman, sarin, and cyclosarin). Its principal use as a chemical warfare agent was in conjunction with other agents (often mustard gas) to form compounds that had lower melting points and were suitable for use in colder weather. It was sometimes also used as a simulant for G-series agents in military research. Today it has medical uses as an anticholinesterase treatment for the miosis associated with glaucoma and as a targeted protease inhibitor against some viral infections. It is also used as a potent insecticide in agricultural settings.

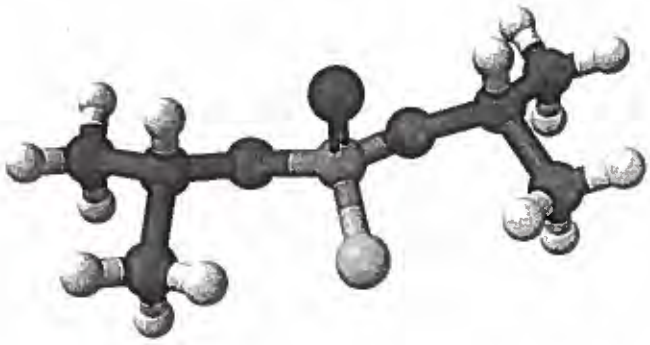


Figure A-18. Structure of Diisopropyl fluorophosphate (DFP). Credit: Ben Mills, 2013.

Malathion (CAS 121-75-5)

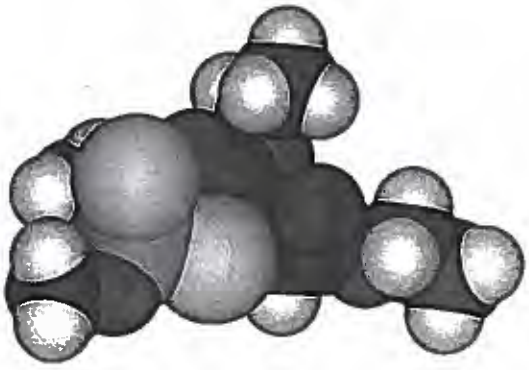


Figure A-19. Space-Filling Model of Malathion

Malathion is a pesticide that is widely used in agriculture, residential landscaping, public recreation areas, and in public health pest control programs such as mosquito eradication. It has been used in Mediterranean fruit fly and West Nile virus control programs, and is also used as a personal pesticide for lice infestations. It is an organophosphate parasympathomimetic which binds irreversibly to cholinesterase (ChE). Malathion itself is of low toxicity, however, absorption or ingestion into the human body readily results in its metabolism to malaoxon, which is substantially more toxic. In studies of the effects of long-term exposure to oral ingestion of malaoxon in rats, malaoxon has been shown to be 61 times more toxic than Malathion.[428]

Physostigmine (CAS 57-47-6)

Physostigmine is a parasympathomimetic alkaloid, specifically, a reversible cholinesterase inhibitor. It occurs naturally in the Calabar bean, native to West Africa. It was synthesized for the first time in 1935 by African-American chemist, Percy Lavon Julian, in conjunction with Josef Pikl.

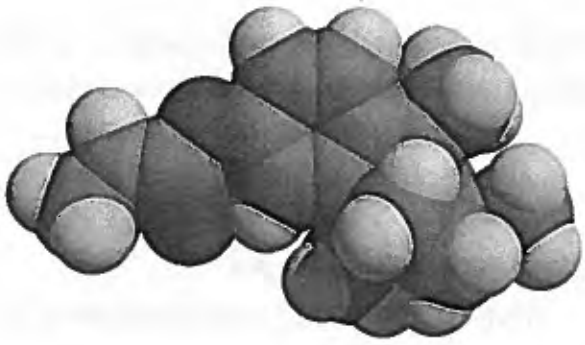
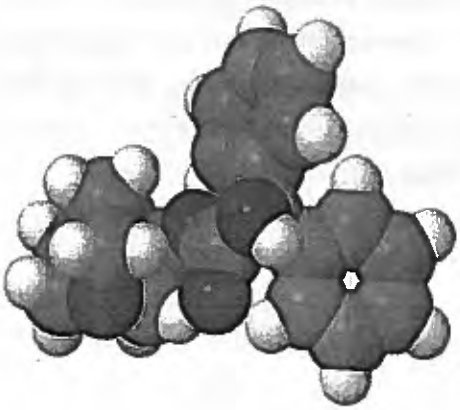


Figure A-20. Space-Filling Model of Physostigmine. Credit: Jacopo Werther

Because it is a tertiary amine, it can cross the blood–brain barrier. Physostigmine salicylate is used to treat the central nervous system effects of atropine, scopolamine, and other anticholinergic drug overdoses. However, routine use not recommended because of potentially serious adverse effects (e.g., seizures, bronchospasm, bradycardia, and asystole).

Anticholinergics

Tox Number B001: 3-Quinuclidinyl benzilate (BZ, QNB)



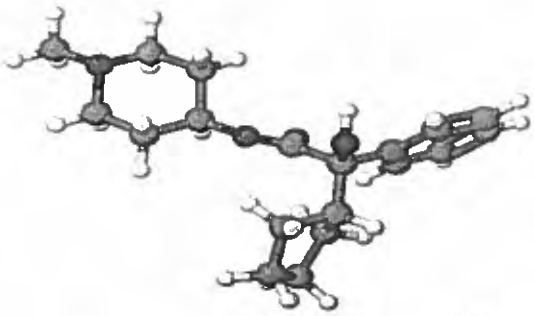
Tox Number B001: 3-Quinuclidinyl benzilate (BZ, QNB)

One of the first incapacitants investigated for use was 3-quinuclidinyl benzilate, also known as QNB or BZ. It is one of the most potent anticholinergic psychomimetics known, and works by competitively inhibiting acetylcholine at postsynaptic and postjunctional muscarinic receptor sites in smooth muscle, exocrine glands, autonomic ganglia, and the brain. Because of its muscarinic receptor target, it has both important parasympathetic and central nervous system (CNS) effects. Its CNS effects include stupor, confusion, and hallucinations, sometimes lasting for days depending upon the dose. The onset of action is approximately 1 hour, post-exposure with peak effects occurring 8 hours post-exposure. Acute symptoms gradually subside over 2-4 days. BZ can be delivered as an aerosol, or prepared with carrier substances for gastrointestinal or percutaneous absorption.

Estimates of the aerosol doses of BZ required to produce mild incapacitation (blurring of vision, minimal lack of coordination) is 66-124 mg.min/m^{-3}. Moderate incapacitation, which includes confusion, hallucination, and incoherent speech was achieved with 102-152 mg.min/m^{-3}, and severe incapacitation, which could include stupor or coma, resulted from doses of 110-165 mg.min/m^{-3}.

Use of QNB has been suggested, but not confirmed, in two past international conflicts: In 1992 in the Mozambican Civil War, and in 1995, in Bosnian War. It also is used in low-levels as an illicit, recreational drug in some civilian populations.

Tox Number B002: N-Methyl-4-piperidyl cyclopentylphenyl glycolate



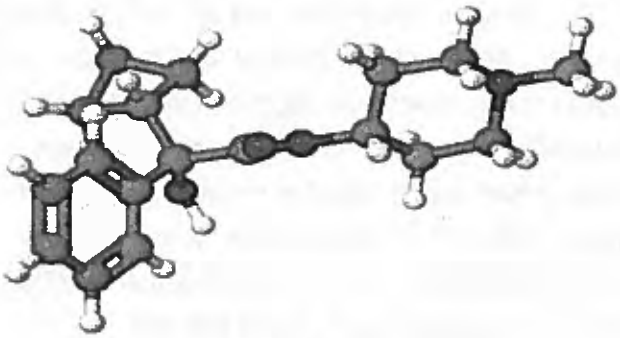
Tox Number B002: N-Methyl-4-piperidyl cyclopentylphenyl glycolate

N-Methyl-4-piperidyl cyclopentylphenyl glycolate is one of the glycolate esters closely related to BZ. Notably, its incapacitating dose is two-thirds that of BZ. It also has fewer effects on the peripheral nervous system than BZ, but produces more central nervous system effects, such as hallucinations. Almost all of the recent unclassified information available on this compound comes from publications reviewing historical human exposure testing data by the U.S. military, or from publications older than the scope of this report (1960s-1970s).[429] It is not a compound currently in clinical or commercial use. (See Table A-3.)

Table A-3. The Potency of Tox Number B002 Relative to BZ [15 (Moshiri)]		
ID_{50}	Relative Potency	
µg/kg (relative to BZ; BZ=1)	Peripheral Effects (BZ=1)	Central Nervous System Effects (BZ=1)
3.4 (0.65)	0.43	1.6

Tox Number B003: N-methyl-4-piperidyl cyclobutylphenyl glycolate

N-methyl-4-piperidyl cyclobutylphenyl glycolate is another one of the glycolate esters closely related to BZ. Its incapacitating dose is about three-quarters that of BZ. Like Tox B002, it has about half as many peripheral effects as BZ, but produces one and a half-times as many central nervous system effects. Almost all of the recent unclassified information available on this compound comes from publications reviewing historical human exposure testing data by the U.S. military, or contemporaneous academic and civilian studies. It is not a compound currently in clinical or commercial use. There was no information available about potential long-term sequelae of exposure. (See Table A-4.)

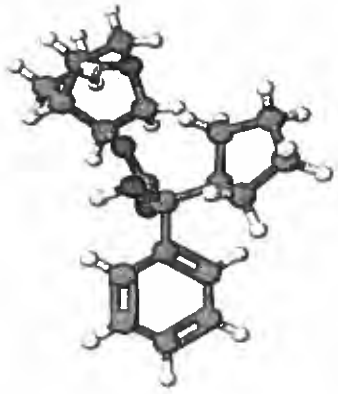


Tox Number B003: N-Methyl-4-piperidyl cyclobutylphenyl glycolate

Table A-4. The Potency of Tox Number B003 Relative to BZ [15] (Moshiri)		
ID_{50}	Relative Potency	
µg/kg (relative to BZ; BZ=1)	Peripheral Effects (BZ=1)	Central Nervous System Effects (BZ=1)
3.9 (0.75)	0.48	1.5

Table A-5. The Potency of Tox Number B006 Relative to BZ [15] (Moshiri)		
ID_{50}	Relative Potency	
µg/kg (relative to BZ; BZ=1)	Peripheral Effects (BZ=1)	Central Nervous System Effects (BZ=1)
4.1 (0.78)	0.37-0.74	1.4

Tox Number B006: 3-quinuclidinyl phenylcyclopentyl glycolate

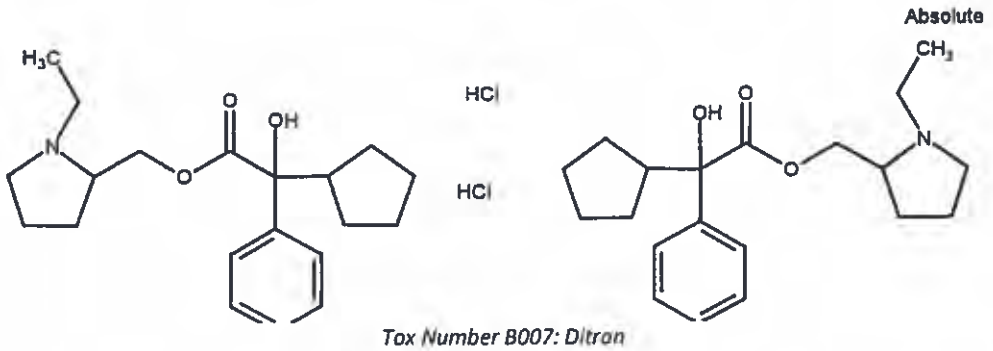


Tox Number B006: 3-Quinuclidinyl phenylcyclopentyl glycolate

Another analogue of BZ that was tested for its incapacitating effects was 3-quinuclidinyl phenylcyclopentyl glycolate. According to tests performed by the U.S. military at Edgewood, cited in JD Ball's review article, this compound had a lower incapacitating dose than BZ, along with fewer effects on the peripheral nervous system. Conversely, it had more central nervous system effects than BZ, and effects from exposure could be detected for up to five days after exposure, a full day after BZ's symptoms had usually ceased. (See Table A-5.)

Tox Number B007: Ditran (JB-329, CAS: 8015–54–1)

Ditran is an anticholinergic drug mixture that is also related to BZ. It is composed of a mixture of 70 percent 1-ethyl-2-pyrrolidinylmethyl-alpha- phenylcyclopentylglycolate and 30 percent 1-ethyl-3-piperidyl-alpha-phenylcyclopentylglycolate. These compounds are structural isomers and have very similar pharmacological properties. The piperidine compound is the more potent of the two and the reason the mixture was used was because of ease of manufacture. It is also possible to make the piperidine compound in its pure form, so there were ultimately two forms of Ditran used in research, the original 70/30 mix, and "Ditran-B", the pure piperidine compound.

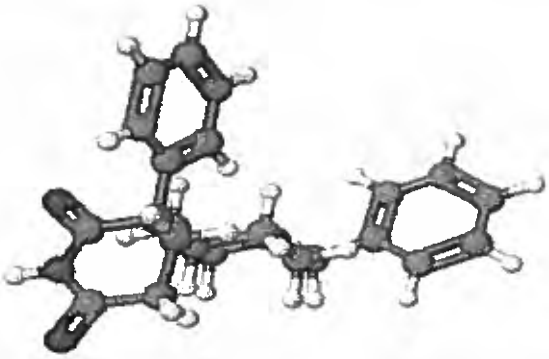


Tox Number B007: Ditran

Ditran was developed in an attempt to produce non-lethal incapacitating agents similar to BZ, but was found to be less potent. It was, however, roughly comparable to the action of atropine and scopolamine, although scopolamine was the most potent of the three drugs. Ditran fell out of use, and most research on it stopped by the 1980s.

The only recent publication discussing Ditran that could be found is on its historical use in toxic, antipersonnel projectiles (bullets, shells, etc.).[267]

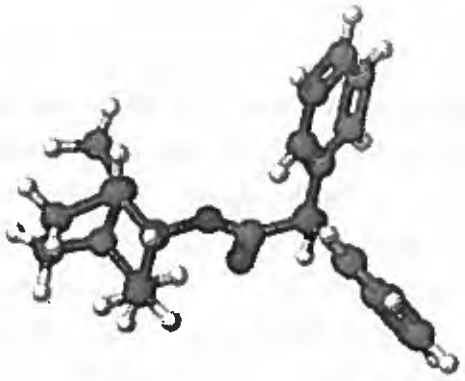
Tox Number B008: Benzetimide HCl



Tox Number B008: Benzetimide HCl

Benzetimide HCl is a powerful anticholinergic that was investigated both as an incapacitating agent and as an anti-Parkinson's disease medication. It produced neuromuscular blockage without anesthesia, and decreased peripheral nerve sensation. In increasing doses, it could produce tremor, seizure, and convulsions. Like other anticholinergics, mydriasis (dry eyes) and pupil dilation were side effects.

Tox number B009: L-2-α-tropinyl benzilate hydrochloride



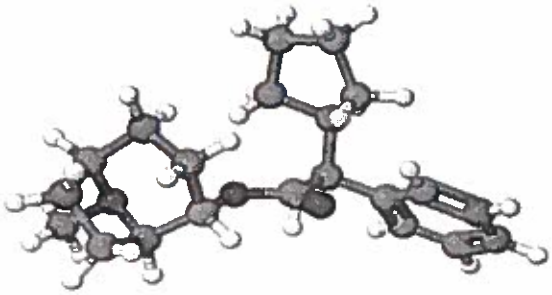
L-2-α-tropinyl benzilate hydrochloride is an anticholinergic that was investigated as an incapacitating agent because of its central nervous system effects. It produced powerful hallucinations and distorted perceptions at doses as small as 0.007 mg/kg in humans.

L-2-α-Tropinyl benzilate hydrochloride is no longer in widespread clinical or commercial use, and there is no recent scientific or medical information about its effects. A small literature does exist from the 1960s and 1970s, when it was under investigation as an incapacitant.

Tox Number B010: L-2-α-tropinyl L-cyclopentylphenylglycolate

L-2-α-tropinyl L-cyclopentylphenylglycolate was tested on approximately twenty-one human subjects in the late 1960s to evaluate its effects as an incapacitating agent in order to learn how to better protect U.S. servicemen from its effects.

It was a notable substance because it had powerful central nervous system effects that were more than two and a half times those of BZ at only one-tenth the dose. It had, however, fewer effects on the peripheral nervous system than did BZ.



Tox Number B010: L-2-α-Tropinyl L-cyclopentylphenylglycolate

Testing was limited, and there is very little information about the compound in current literature. The one recent paper that discusses it, does so to review historical work on the compound. (See Table A-6.)

Table A-6. The Potency of Tox Number B010 Relative to BZ [15] (Moshiri)

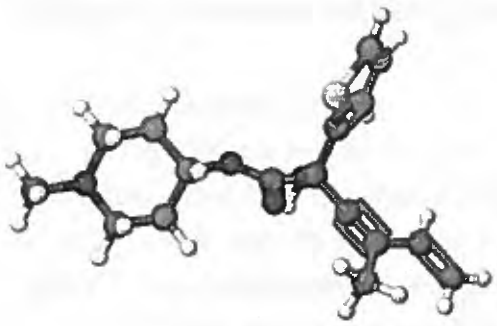
ID_{50}	Relative Potency	
µg/kg (relative to BZ; BZ=1)	Peripheral Effects (BZ=1)	Central Nervous System Effects (BZ=1)
2.0 (0.12)	0.37-0.74	2.5

Tox Number B011: N-methyl-4-piperidyl cyclopentylmethyl-ethynyl glycollate (PCMG)

N-methyl-4-piperidyl cyclopentylmethyl-ethynylglycollate or PCMG was a moderately potent and relatively short lasting anticholinergic deliriant drug, related to the chemical warfare agent BZ. It was developed under contract to Edgewood Arsenal during the 1960s as part of the U.S. military chemical weapons program, during research to improve upon the properties of earlier incapacitants agents. During research and development PCMG was found to be only around one-fourth the potency of BZ, but its onset of action was much faster - only a few minutes. Additionally, in a dose-dependent manner, duration of effects could be far shorter – at only 2-3 hours. A fast-acting and short-lasting anticholinergic drug was felt to be more desirable for some applications.[430]

Tox Number B012: cis-2-methyl-3-quinuclidinyl cyclopentylphenyl-glycolate

The only information that could be found on Tox Number B013 was a Chem ID-Plus Datasheet from ToxNet. Although this provided some structural and chemical properties, no toxicity data was available.

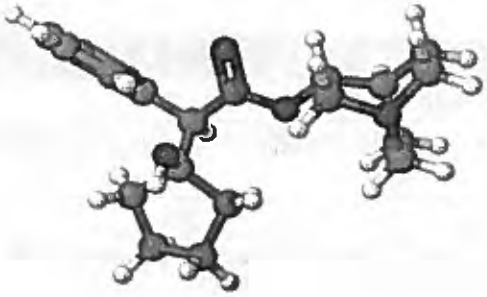


Tox Number B013: 1-Methyl-4-piperidyl phenyl-(3-methylbut-1-yn-3-enyl)-glycolate

Tox Number B013: 1-methyl-4-piperidyl phenyl-(3-methylbut-1-yn-3-enyl)-glycolate

This unusual anticholinergic was tested on only eight servicemen at Edgewood/Aberdeen. There is no information available in recent publications about this compound. A Chem-ID Plus fact sheet from ToxNet only revealed that the LD_{50} for mice was 36 mg/kg delivered as an intravenous dose. No further information is available as the compound is not in widespread use today.

Tox Number B014: 3-quinuclidinyl (1-hydroxycyclopentyl) phenylacetate



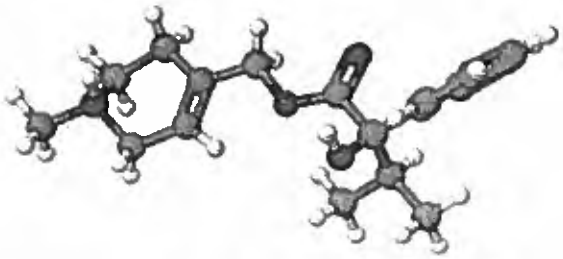
Tox Number B014: 3-Quinuclidinyl (1-hydroxycyclopentyl) phenylacetate

Only five servicemen at Edgewood/Aberdeen were exposed to this anticholinergic compound. There is little information about it, except that it has an extremely low intramuscular toxic dose for humans of 0.003mg/kg.

Tox Number B015: 3-quinuclidinyl cyclopentyl-(2 –propenyl)-glycolate

This anticholinergic was tested on 18 servicemen during the human exposure trials at Edgewood/Aberdeen. Other than a Chem-ID Fact sheet, only historical animal testing information remains. In original reports form Edgewood, it is noted to have had a potency more or less the same as that of BZ, however, it's time to action was extremely short as were the duration of its effects.

Tox Number B016: 4-(1-methyl-1,2,3,6-tetrahydropyridyl)-Methyl-Isopropyl-phenylglycolate



Tox Number B016: 4-(1-methyl-1,2,3,6-tetrahydropyridyl)-Methyl-Isopropyl-phenylglycolate

Thirty-nine servicemen were administered Tox Number B016 during the Edgewood/Aberdeen exposure tests. Subjects were given a range of doses from 1.0 to 4.6 µg/kg via the intravenous route. When scored against baseline performance on Numbers Facility Test, all subjects lost at least 25 percent of their abilities, and men given the largest doses lost as much as 50 percent of their baseline abilities. The intravenous ID_{50} was estimated to be about 9 µg/kg based on both performance on a Numbers Facility Test and clinical evaluation of the test subjects. (See Table A-7)

Table A-7. The Potency of Tox Number B016

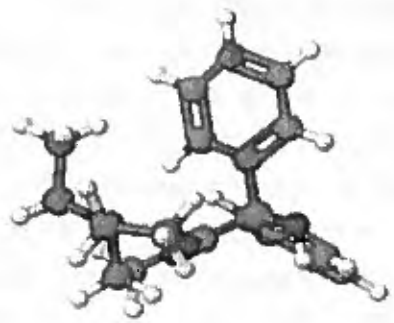
ID_{50}	Relative Potency	
µg/kg	Peripheral Effects	Central Nervous System Effects
8.9	0.9	2.4

**Peripheral potency is in comparison to atropine (based on ED_{50} to produce maximal heart rate of at least 100 beats/min.). Central potency is in comparison with scopolamine (based on ID_{50}).*

Tox Number B018: Benactyzine HCl (Amizil, Suvatil, Parasan, Nutinal)

Various benactyzine compounds were tested for psychomimetic effects by the U.S. military. A total of sixteen servicemen were given the drug. Those given low doses noted a feeling of detachment from reality. Those given moderate doses had frequent episodes of forgetfulness while the drug was active, and those given higher doses experienced euphoria and hypersensitivity with some hallucinations.

In addition to these tests, benactyzine was used for decades for treatment of depression and related anxiety, until it was removed from the U.S. market by the Food and Drug Administration for lack of effectiveness. It is still used as an anticonvulsant used to treat Parkinson's disease.



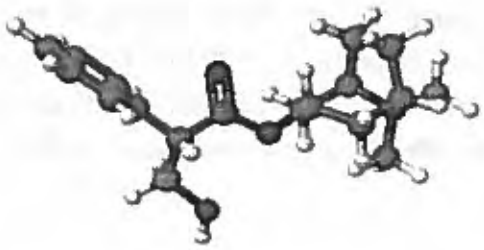
Tox Number B018: Benactyzine HCl

Recent work in chemical defense has suggested benactyzine as an adjunct treatment for organophosphate nerve agent poisoning. It has shown to be effective in stopping convulsions in animals. Benactyzine stopped convulsions brought on by the administration of sarin or soman, even after the test animal had been convulsing for more than 30 minutes.[431,432]

Recent *in-vitro* analyses of the action of benactyzine on the survival of cell lines found that it had very low toxicity when compared with other anticholinergics such as atropine and obidoxime. Likewise, the same study found low levels of DNA damage by benactyzine administration relative to the damage caused by the other drugs.[433]

Tox Number B022: atropine methyl nitrate (Eumydrin)

Atropine methyl nitrate (AMN) is a synthetic atropine and a muscarinic cholinergic blocker that does not cross the blood brain barrier. It produces all of the peripheral effects of atropine, but none of the centrally-mediated ones. Peripheral effects could include rapid heart rate, dry mouth and eyes, blurred vision and lack of balance and coordination. In high doses it can incapacitate just like atropine.



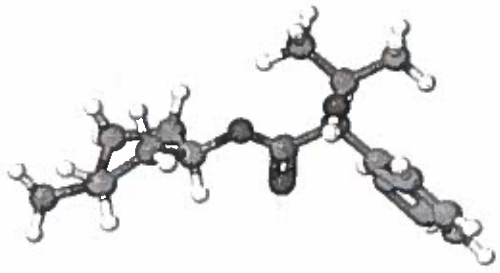
Tox Number B022: Atropine Methyl Nitrate (Eumydrin)

A total of 18 servicemen underwent 50 exposures of AMN or Eumydrin during the Edgewood/Aberdeen human trials of anticholinergic compounds. Very little information is available about these tests except that the human intramuscular toxic dose was calculated to be 0.002mg/kg.

Studies examining the potential effects on cognition of atropine compounds have found that atropine, but not AMN has an inhibitory effect on some types of learning and memory.[434] The researchers believe that AMN does not have an effect on cognition because the neurobehavioral elements studied are centrally mediated and AMN only acts on peripheral muscarinic targets.

Tox Number B023: N-methyl-4-piperidyl isopropylphenyl-glycolate (EA 3834)

EA 3834 is somewhat distinctive from the other anticholinergic test compounds. The intravenous ID_{50} is approximately 5.7 µg/kg, which is about the same as that for BZ. However, the time of onset of severe effects of EA 3834 is inversely related to dose. Onset of symptoms occurs after about 35 min for subject given the ID_{50} and after about only 10 minutes for those administered 3 times the ID_{50}. The duration of severe effects is roughly constant within this dose range, and usually begins to taper off after six to nine hours. A total of 144 servicemen received EA 3834 during the human exposure tests by the U.S. military.



Tox Number B023: N-Methyl-4-piperidyl isopropylphenyl-glycolate (EA 3834)

Possible renal toxicity in two servicemen was reported in the Edgewood studies after the use of this compound.[387] One volunteer who had received the agent intravenously had red blood cells in his urine shortly after the completion of his test. Extensive workup failed to uncover any definite kidney disease or lesion to account for the bleeding, which persisted intermittently for a year after exposure. Animal studies suggested that such bleeding could indeed result from administration. When greater care was taken with screening for renal toxicity or injury, no further cases were noted. Thus, it is not clear whether renal injury was caused by the compound or by the catheterization procedure.

Tox Number B025: toxogonin-atropine-benactyzine (TAB)

TAB is an anticholinergic compound mixing atropine and benactyzine with a third oxime compound, which varies. Today the third compound is often the TMB-4, in the past it has sometimes been 2-PAM, or toxogonin (obidoxime). It is used as a fast-acting medical countermeasure to organophosphate anticholinesterase exposure. From 1975–1980 the U.S. military also used TAB. Prior to use, this TAB (with TMB-4) was tested on 24 servicemen at Edgewood/Aberdeen. Overall, TAB was deemed to be as safe and as effective as atropine alone, although the combination was quicker acting.

Lysergic Acid Diethylamide

Lysergic acid diethylamide, or LSD is a drug of the ergoline family, well known for its psychological effects including hallucinations, synesthesia, an altered sense of time, and spiritual experiences. It is produced by the alkaline hydrolysis of ergotamine, a chemical derived from ergot, a grain fungus that typically grows on rye. LSD can also be synthesized without the use of ergotamine.[435] The drug is very unstable in its pure basic or free-base form (EA 1729), but is relatively

stable as a salt. The two most commonly encountered LSD salts are maleate salt (EA 3528) and tartrate salt (EA 1653) (See Table A-8) Related compounds include the lysergamides, which are amides of lysergic acid; ergotamine is a lysergamide. Several well-known lysergamides include acetyl-LSD (ALD/N-acetyl LSD) and bromo-LSD (BOL-).

LSD has been used to study psychotic-like states and model psychosis[436,437] and as a treatment for psychological disorders. It has also been investigated for the treatment of alcoholism,[438] addiction,[439] cluster headache,[440] and anxiety associated with terminal illness.[441]

It was first synthesized in 1938, by Swiss biochemist Albert Hoffman, while researching compounds to act as respiratory and circulatory stimulants. The discovery took place in the Sandoz laboratories in Basel, but was set aside for several years while work on other, more promising compounds proceeded. Hoffman began work on LSD again in 1943, and accidently discovered its psychological effects after getting some of the drug on his fingertips. After Hoffman's initial discovery and explorations of LSD's hallucinogenic properties, WA Stoll, the director of the laboratory that Hoffman worked in, began experimenting on the psychological phenomena produced by the drug.[442]

Table A-8. LSD and Related Compounds

Lysergic Acid Diethylamide/CAS 50-37-3
• LSD (free base)/EA 1729
• LSD (maleate and tartrate salts)/EA 3528 and EA 1653
Lysergamides
• Acetyl-lysergic acid diethylamide/ALD/N-acetyl LSD
• Bromo-lysergic acid diethylamide/BOL/CAS 478-84-2

Using both normal and psychologically disturbed subjects, Stoll reported changes in perception that led to hallucinations, acceleration of thinking, and slight dimming of consciousness without the lessening of judgement in his subjects. He noted that LSD was outstanding in producing a clear-cut blunting of the effect and suspiciousness that was often seen in schizophrenic patients. In 1947, Stoll and Hoffman patented LSD for psychiatric use under the trade name *Delysid*.[443]

National Security Human Tests with LSD

In 1949, L. Wilson Greene, Edgewood Arsenal's Scientific Director, wrote an influential paper titled *Psychochemical Warfare: A New Concept of War*. In it, he called for a search for compounds that would create the same debilitating effects as nerve gas, developed by the Germans in WWII, but without the lethality.[444] Greene said that, "I am convinced that it is possible, by means of the techniques of psychochemical warfare, to conquer an enemy without the wholesale killing of his people or the mass destruction of his property."

By 1950, attempts to replicate Stoll's findings were taking place at Washington University Medical Center in Saint Louis. The point of these studies were to try to, "reactivate," chronically depressed, or psychotically withdrawn patients.[445] At around the same time, other institutions were exploring the use of LSD in treating other psychological disorders – including Parkinson's disease and a variety of psychoses.

In early 1951, reports that the Soviets were experimenting with psychotropic drugs, including one called, "ketjabung," that rendered subjects unable to resist the control of external handlers began to worry the U.S. Intelligence Community.[446] Also at this time, two Soviet-bloc agents were apprehended at the West German border with vials of an alkaloid compound said to have the same effects as ketjabung, [4] the Soviets made large purchases of ergot, and Polish radio urged citizens to collect ergot as large supplies were needed.[447]

The threat of Soviet experimentation on mind control and incapacitation, as well as civilian findings on LSD effects spurred the Central Intelligence Agency's interest, and in late 1951, their investigations into the drug's effects began.[448] The CIA's efforts were twofold; they wanted to clarify the potential threat to operatives to know how to defend against it, and they wanted to see if the drug could be used offensively to incapacitate or to ease interrogations.

Throughout the rest of the 1950s, interest in the effects of LSD grew amongst civilian medical and scientific groups, and in the U.S. National Security community. In 1960, Sidney Cohen of UCLA compiled the test results of 44 civilian investigators and found that a total of 5000 individuals were administered LSD in the U.S.[449] Similarly, almost 4,500 civilians in the UK were given the drug as part of private medical experiments or as part of a treatment regimen.[450]

The Chemical Warfare Laboratories at Edgewood received authority to use human volunteers in psychochemical drug experiments in May 1956, and later that year, the Medical Research Laboratories at Edgewood began studies on the effects of LSD.[451] Careful candidate selection with a barrage of medical and psychological tests occurred and individual consent from subjects was required. All tests were performed under medical supervision. Retrospective analysis of the health effects of LSD conducted by the Department of the Army identified 741 individuals thought to have participated in the LSD tests.

Oximes

Organophosphorus chemicals (OPs) and anticholinesterase chemical warfare agents (CWAs) inhibit acetylcholinesterase (AChE) at synaptic junctions by depositing a phosphoryl group at the

enzyme's active site. This results in an accumulation of acetylcholine and uncontrolled activation of cholinergic synapses. Oximes are chemicals that react with the cholinesterase enzyme inhibited by the OPs and CWAs, and allow acetylcholinesterase to break down acetylcholine.

The ability to reverse acetylcholinesterase inhibition varies with the OP, CWA exposure, and route of administration. Timing of oxime administration is critical because the binding of the nerve agents to a cholinesterase can become irreversible with time ("aging"). Once aging has occurred, the cholinesterase enzyme will be unable to break down acetylcholine. Aging occurs at different rates for different nerve agents. Aging can sometimes be counteracted with continuous or intermittent doses of oxime as opposed to single bolus dosage. Soman's rapid aging, however, still makes treatment of this CWA challenging.

Oximes are often administered with atropine and complement the function of this anticholinergic compound, which is a potent muscarinic antagonist, whereas oximes work mostly at nicotinic synapses. Oximes also tend to act peripherally because their ability to penetrate the blood brain barrier can be limited (depending on the oxime type and plasma concentration).

Historical work has shown that some of the acute toxic effects of oximes are due to the generation of cyanide through metabolic processes.[452,453] However, existing data suggest less than 5 percent of administered doses is converted to cyanide, and this does not represent a significant health threat in animals. It is not known whether this is also true for humans and other primates. Another pathway for oxime toxicity may be related to their ability to form compounds with the OPs they remove from AChE binding sites (phosphylated oximes).[454]

Some of these compounds are more stable than others, and those formed by obidoxime and trimedoxime are more stable than those formed by pyridoxime.[455] These compounds are important because they may have higher AChE inhibition rates than OPs themselves. This, however, varies greatly by OP exposure and oxime.[456]

Toxogonin, Obidoxime chloride

Obidoxime was developed in Germany in the early 1960s and introduced into medical practice as a treatment for OP poisoning. Being a good AChE reactivator, obidoxime, given with atropine, efficiently protected experimental animals against poisoning with tabun, sarin, and VX. However, like the pyridoximes and trimedoxime, it was inefficient in countering soman poisoning in mice and other laboratory animals. An exception to this finding was that it could provide some protection against soman in guinea pigs that were pretreated with the anticholinergic pyridostigmine.[457]

Trimedoxime (TMB4)

TMB-4 was first synthesized in the late 1950s and was the first bispyridinium oxime to be effective against tabun (GA) exposure.[458] Historical studies from the 1970s have described the side effects of TMB4 after intramuscular injection of 250 mg (2.5 -3.52 mg/kg) in humans.[459, 460] Acute adverse reactions included a burning sensation at the site of injection, warm sensation in the face, dizziness, blurred vision, difficulty concentrating, headache, diplopia, impaired accommodation, and nausea. Symptoms were of variable duration and lasted from 10 to 45 minutes.

A more recent examination of symptoms produced by accidental injection with atropine and TMB4 autoinjectors in Israel, however, found no adverse reactions related to TMB4 exposure in adults.[301] This study was based on data collected from the Israel Poison Information Center, and the Assaf Harofeh Medical Center over a two-year period. The absence of adverse effects in the study subjects was likely related to the lower dose of TMB4 in the autoinjectors (80 mg) relative to the dosages used in the earlier study (187 – 262 mg). These results are similar to those found in a historical (2005) study in which children receiving unintentional injections from atropine and TMB4 autoinjectors experienced no significant adverse side effects of injection.[461]

Pralidoxime methane sulfonate

Pralidoxime is the most frequently used oxime worldwide and occurs in four forms: Pralidoxime chloride [2-PAM; molecular weight (MW) 173]; Pralidoximemesylate (P2S; MW 232); Pralidoxime metilsulfate (MW 248), and Pralidoxime iodide (MW 264).[462]

The different salts vary in efficacy according to the chemical characteristics of the salts. For example, the lower molecular weight of the chloride salt provides 1-5 times more active compound per gram than does the larger MW iodide salt.[463] The effectiveness of the different pralidoxime compounds and of other oximes as well, can also vary depending upon the specific OP or CWA exposure.

First discovered in the mid-1950s, pralidoxime was soon successfully introduced into clinical practice for patients with organophosphate pesticide poisoning. Despite the beneficial effects of pralidoxime first noted with parathion poisoning, its effectiveness has been much debated. Historical trials in the developing world, where OP poisoning is an important public health problem, noted that low-dose infusions of pralidoxime may actually increase morbidity and mortality in patients.[302,303,304] A recent meta-analysis by Buckley and Eddleston, however, suggested that these clinical trials used suboptimum doses and inadequate delivery regimes of pralidoxime, that investigators did not achieve the plasma concentrations of oxime recommended by

the World Health Organization, and that these design issues were the cause of their poor outcomes.[305]

A more recent clinical trial by Pawar examining the efficacy of high-dose pralidoxime for OP poisoning found the administration of the oxime improved morbidity and treatment outcomes.[306] In that trial, patients were given a dose of oxime upon admission and were then randomly assigned to control and study groups (100 patients per group.) Controls were given a bolus dose of 1 g pralidoxime per hour every 4 hours for 48 hours. The study group had a constant infusion of 1 g per hour every hour for 48 hours. Patients receiving the high-dose pralidoxime regimen required less atropine during the first 24 h than controls [median 6 mg vs 30 mg; difference 24 mg (95% CI 24-26, $p < 0.0001$)]. Eighty-eight percent of controls and 64 percent of high-dose patients needed intubation during admission to hospital (relative risk = 0.72, 0.62-0.86, $p = 0.0001$). Control patients required ventilatory support for longer [median 10 days vs 5 days; difference 5 days (5-6, $p < 0.0001$)].[306]

Irritants

The irritant compounds cause tearing, rhinorrhea, intense salivation, and irritation of the skin and eyes, and are commonly known as, "tear gasses," or lachrymatory agents. Brief exposure to irritants produces effects that generally resolve within an hour, leaving no long-term sequelae. However, sustained exposure to high concentrations may produce tissue injury, notably to the eye, respiratory tract, and skin.[314]

Because irritant compounds generally produce only transient casualties, they are widely used for riot control and situations where long-term incapacitation is unacceptable. When used against poorly equipped disruptive or enemy forces, these compounds have proved extremely effective in dispersing crowds and quelling disturbances. When released indoors, however, they can cause serious illness or death.[464]

Today, commonly used irritants include: CN (chloroacetophenone), CS (chlorobenzylidene malononitrile), CR [dibenzoxazepine), and OC (oleoresin capsicum-based compounds (or pepper sprays)]. Many police and military units mix irritants as well, so it would not be uncommon for CS and pepper-spray to be used together to disperse potentially violent or disruptive crowds.[465] Irritants are generally dispersed into the atmosphere as pyrotechnically generated smokes, aerosols, vapors, or dusts. They may also be dispersed in solution as jets or sprays with the solution chemicals chosen for their own irritant effects.[465]

(CA) Bromobenzyl cyanide

CA was one of the first tear agents or lacrimators fielded in-theatre in World War I. After the war, CA fell out of favor in the west because it was considered too toxic and was generally replaced with CN-series agents.[466] Its use, however, persisted in the Soviet Union and satellite nations, where it was sometimes mixed with mustard gas or bis(chloromethyl) ether.[467] It is now considered obsolete, but was tested on 13 volunteers at Edgewood Arsenal in 1966, to study its persistence in enclosed spaces, as well as its effects on human subjects.[405]

(CN) Chloroacetophenone

CN was developed at the end of World War I, but it came into use after the war, and in the interwar years, it became widely used by militaries and law enforcement agencies around the world. Also known as Mace ™ when it is dispensed as a low-dose, pressurized aerosol, CN produces a burning sensation in the nose, eyes, and mouth followed rapidly by tearing, rhinorrhea, and salivating. Burning sensation on exposed skin is also a common acute effect. (See Table A-9.)

Table A-9. Comparison of the Estimated Human Toxicity of CN and CS [468, 469]

	(CN) chloroacetophenone	(CS) chlorobenzylidene malonitrile
Threshold for eye irritation (mg/m3)	1.0	0.004
Effective concentration—ICt50 (mg/min/m3)	20–50	4–20
Estimated lethal dose—LCt50 (mg/min/m3)	8500–25 000	25 000–100 000

Older animal studies (rat, rabbit, guinea pig and mouse) from the 1970s examining the inhalational pathophysiology and pathogenesis of CN at LD_{50} exposures found that the lungs of exposed animal were macroscopically congested, edematous, and had multiple variable sized hemorrhages. Histopathology of the lungs showed congestion of alveolar capillaries intrapulmonary veins, intra-alveolar hemorrhages, bronchioles occluded with excess secretions, and patchy acute inflammatory cell infiltration of the trachea, bronchi, and bronchioles. Importantly however, animals sacrificed 14 days post-exposure, in general, showed no pathology. So, animals surviving intentionally high initial doses sustained only acute injury, not long-term serious damage.[307]

(DM) Adamsite

Adamsite is an arsenical irritant often referred to as a, vomiting agent. Its effects are, however, largely similar to CN, CS, and several other irritants, although both time to onset of symptoms

and duration are generally longer than in other agents. Within five minutes of exposure to Adamsite as an aerosol, humans feel a burning sensation beginning in the eyes and upper respiratory tract. This can be followed by rapid, uncontrolled blinking and tearing, rhinorrhea and then nausea and vomiting.[470] If exposure to Adamsite aerosol is in an open-air environment, initial symptoms will begin to clear within 20-30 minutes. Historical studies indicated that a second wave of symptoms, including headache, depression, perspiration, chills, nausea, abdominal cramps, vomiting, and diarrhea, may appear about 30 minutes after exposure and persist for several hours.[471]

EA 1778 (nonanoyl morpholide), MPK

Nonanoyl morpholide or EA 1778 was an irritant agent developed at Edgewood Arsenal. It is a synthetic compound of capsaicin, which acts as a lacrimator or tearing agent and causes coughing, a burning sensation of the nose, throat, and eyes, and in some cases nausea. It has also been reported to cause respiratory tract irritation including rhinorrhea, substernal pain, and dyspnea. It is not a persistent agent, and symptoms were relieved when subjects were allowed to breathe fresh air.[472]

Commercially, EA 1778 is available as an aerosol canister for the Russian UDAR ("punch") gun used by both military and civilians as an antipersonnel weapon.[325]

(CS) Chlorobenzylidene malononitrile

CS is widely used around the world for crowd control and is generally dispersed as a grenade-generated smoke, as a droplet aerosol, or as a liquid solution. Commercial CS-based products include Paralyzer® and the mixture of CS and capsaicin known as Sabre®. Historical studies examining human response to liquid exposure found that after drenching with 0.001–0.005% CS in aqueous 3.3% glyceryl triacetate, there was an abrupt onset of stinging sensation of the eyes, uncontrolled blinking and tearing, all persisting for about 3 minutes. This was followed by stinging sensation of the skin, progressing down from the face to neck, back, and genitalia. Skin discomfort resolved within about 10 minutes.[473]

EA 2097, Benzylidene malonitrile

Benzylidene malonitrile is the parent compound of the CS agents (-chlorobenzylidene malononitrile). Lindsay and colleagues have recently recounted historical trials at Porton Down that exposed human volunteers to various benzylidene malonitriles (BMNs).[474] That paper stated, "BMN is an irritant which attacks the respiratory tract and to a lesser degree the eyes. In both respects, however, it is far less potent than many other well-known compounds."

In these Porton Down tests, the men who were exposed became affected within 1 minute and experienced mild coughing and restricted breathing. There was also tear formation but no actual lachrymation. Although this concentration would interfere with carrying out ordinary duties, the symptoms could not be described as indicating the limit of tolerability during an exposure of 3 minutes. Towards the end of the exposure, the discomfort was subsiding.[474]

(CR), EA 3547, Dibenzoxazepine

Dibenzoxazepine is a potent irritant that is 5-10 times more effective than CS but is much less toxic than CS or CN (human LCt_{50} is estimated at > 100,000 mg.min/m^3).[475] CR causes an immediate irritation of the eyes, nose, and skin, and its effects are nearly identical to CS but generally more transient. CR is also the parent compound to loxapine, which is related to the antipsychotic drug Loxitane (loxapine succinate).[476] Because of this association, CR may produce a decline in aggressive behavior.

Despite its reduced toxicity in humans, CR is not entirely without long-term risk. CR is fairly stable, resists weathering, and persists in the environment for long periods of time.[477] For example, Kovalev et al., studied the persistence of CR on cotton fabric and found that storage conditions greatly influenced the persistence of CR on the fabric.[478] That study found that after 300 days post exposure, CR on the fabric stored in the open had reduced to 22.5% of original values, while that on the fabric stored in closed conditions was reduced only 79%. After 600 days, the values of CR on the fabric were 3% and 52 % for open storage conditions and closed storage, respectively. Additionally, the same group of researchers showed that CR on fabric stored in closed conditions cause severe eye irritation in rabbits, even after 600 days post exposure.[479] Because of CRs high persistence, enhanced toxicity may occur with prolonged or repeated exposure, and secondary exposures may occur.[480]

Historical work done on the toxicity of CR in mice, rats, and rabbits found that 14 days after a single, non-lethal exposure to CR in a pyrotechnically generated smoke, half of the animals exposed still had lung pathologies, including intra-alveolar hemorrhages, and moderately advanced bronchopneumonic change.[475]

(CHT), EA 4923, 1-Methoxy-1,3,5-cycloheptatriene

In an effort to make dissemination of irritant agents easier than thermal or pyrotechnic generation of solid compounds CN, CS, and CR, scientists at Edgewood Arsenal developed and tested the volatile liquid agent 1-Methoxy-1,3,5-cycloheptatriene (CHT, 1-MCHT). It has roughly the same acute effects as the other irritants: lacrimation, skin and mucus membrane irritation, is less potent than CR or CS, and is equally as toxic as CR (but less toxic than CS). It also has the

ability to penetrate skin or rubber, and can produce dose-dependent ataxia, tremors, and death via the percutaneous route.[481]

In early toxicity studies performed at Edgewood, McNamara and colleagues, noted that persistent neuromuscular weakness persisted in some dogs for months after percutaneous exposure from a covered patch providing a dose of 500 mg/kg, or from intravenous administration at 10 mg/kg.[482] Rabbits also displayed neuromuscular weakness after cutaneous exposure. Studies done in the 1990s on intravenously dosed dogs showed several histological abnormalities in the brain after exposure. Specifically, there was marked Purkinje cell death and subsequent reactive gliosis in the cerebellum and a few necrotic neurons in the diencephalon, pons, and medulla. These changes possibly underlay the motor disturbances seen in the dogs. The same animals also have hematological abnormalities including leukocytosis with relative lymphopenia, and biochemical changes such as hyperglycemia.[483]

Cole also demonstrated the mutagenic potential of CHT using a modified mouse lymphoma assay. In these tests (using S9 fraction for metabolic activation) CHT was shown to be a clastogenic mutagen, since a dose-dependent increase in micronuclei was observed.[484]

Incapacitants

Incapacitating agents are pharmacological agents that impair the ability of a subject to perform coordinated tasks by decreasing motor activity, conscious state, or by producing tranquilization through mechanisms in the central nervous system.[485] Included in this class of agents are deliriants, stimulants, and depressants, which interfere with higher functions of the brain such as attention, orientation, perception, memory, motivation, conceptual thinking, planning, and judgment.

302089 & 302582, Butyrophenone derivatives

The butyrophenones are a class of antipsychotics that were developed by Janssen Pharmaceuticals in the late 1950s to provide analogs of meperidine using inexpensive chemical substitutions. Although there is no historical or recent technical information available on the specific butyrophenones researched and tested at Edgewood Arsenal in open sources, butyrophenones are still widely used today. Most of the information about toxicology, side-effects, and sequelae are available on haloperidol.

EA 2148-A, Phencyclidine (PCP)

Phencyclidine was originally synthesized and developed as an anesthetic agent for human use. However, it was soon abandoned, because it sometimes produced postoperative psychosis and agitation. Its symptoms include lightheadedness, numbness, confusion, tremors, ataxia and

prostration, and it can be administered to produce effect by intravenous line, aerosol or liquid, by mouth, and through a percutaneous patch.[486]

Phencyclidine has several sites of action in the central nervous system, all of which act synergistically to result in anesthesia and analgesia. It has greatest affinity for the NMDA (N-methyl-D-aspartate) receptor complexes in the hippocampus, neocortex, basal ganglia, and limbic system. PCP also has a decreasing affinity to NMDA receptors, to the neuronal norepinephrine (NE), dopamine (DA), and serotonin (5-HT) reuptake system, and to the σ opioid receptors.[487]

218437, an indolylalkyl piperazine, Oxypertine

Oxypertine is an antipsychotic medication used in the treatment of schizophrenia. An early study of the effects and toxicity of this compound in rats ("Win 18437") compared it with chlorpromazine, the benchmark drug for treating schizophrenia.[488] This study found that 218437 increased (potentiated) hexobarbitone sleeping time, caused hypothermia, and afforded protection from amphetamine toxicity in aggregated mice to a degree comparable with chlorpromazine. However, it noted that 218437 (in the doses administered: 1, 2, 5, and 10 mg/kg) was three-times weaker than chlorpromazine in blocking conditioned avoidance response in rats, and was more toxic.

220548, Benzomorphan

Benzomorphan is the parent compound for a series of drugs which variably act on the opioid and sigma receptors as an analgesic. There are many drugs on today's pharmaceutical market with a benzomorphan base used for pain relief. Several of these were reviewed in the course of the literature search for information on potential long-term sequelae of exposure. The drug best described in the literature is pentazocine and is still widely used (and abused) in the developing world.

302034, Benzomorphan butyrophenone

The morphine-like opioid analgesics such as the benzomorphans were sometimes mixed with other compounds in an attempt to improve their potencies, toxicity profiles, or safety margins. One of the tranquillizing agents researched at Edgewood Arsenal as a potential combinant with the benzomorphans was a butyrophenone (302089).[489]

EA 1476, EA 2233, EA 2233 2-8, Dimethylheptyl pyran

Dimethylheptylpyran (DMHP) is a synthetic analogue of tetrahydrocannabinol (THC), the active component of THC. It was invented in 1949 during attempts to study the structure of THC, but was found to be considerably more potent, and had much stronger analgesic and anticonvulsant effects.[490] DMHP (EA 1476) and its eight stereoisomers (EA 2233, and EA 2233 1-through-

8, 24) were investigated at Edgewood Arsenal from 1958 to 1968. The major signs of DMHP toxicity were: ataxia, analgesia, mydriasis (pupil dilation), and central nervous system depression lasting from several hours to several days. The lethal doses of DMHP were also extremely high in comparison with the small doses required to produce its pharmacodynamic effects. For example, the intravenous LD_{50} in mice is 63 mg/kg, whereas the minimal effective dose in 50% of the animals (ED_{50}) is 0.075 mg/kg. This high margin between the effective and lethal doses was the main reason it was being investigated as a non-lethal incapacitating weapon.

Miscellaneous Traditional Chemical Warfare Agents

Sulfur Mustard

Between 1980 and 1988, more than 100,000 people are estimated to have been exposed to sulfur mustard gas during the Iran-Iraq War.[104] A significant subset of these sulfur mustard victims (< 30,000 people) have had medical follow-ups, in some cases, for over 25 years post exposure.[105,106] Long-term sequelae have been noted in the skin, eyes, and respiratory systems[107, 108] of those exposed, and a wide variety of complaints in the gastrointestinal, endocrine and peripheral nervous systems[109] are also believed to be related to sulfur-mustard exposure. Additionally, genetic alterations, immune dysfunction, neuropsychiatric disorders, and carcinogenesis have been studied.

Phosgene

Phosgene is an irritant to the skin, eyes, and respiratory tract. Exposure often results in severe delayed damage after initial symptoms which include mild irritation of the eyes and throat, with some coughing, choking, feeling of tightness in the chest, nausea and occasional vomiting, headache, and lacrimation. It's more severe symptoms include respiratory and cardiovascular failure, which results from low plasma volume, increased hemoglobin concentration, low blood pressure, and an accumulation of fluid in the lungs.[491]

Lewisite

Lewisite is an arsenical vesicant developed early in the 20th century in an attempt to create a more effective blister agent than sulfur mustard. Like sulfur mustard, it is both a vesicant and systemic poison, but is more rapidly absorbed through the skin.[492] Dermal or intravenous exposure to lewisite leads to local skin or pulmonary edema due to increased capillary permeability. The vesicant properties of lewisite result from direct contact with the skin. Signs of dermal toxicity (pain, inflammation) may be experienced within a minute after exposure. Acute lethality is usually the result of pulmonary injury. Ocular exposure may result in corneal necrosis.[493]

Hydrogen Cyanide

Hydrogen cyanide (HCN) is a poison and classical chemical weapon that has been used on battlefields, in mass executions and suicides and in assassinations. From a public health perspective, cyanide poisoning in humans is most commonly caused by smoke inhalation in fires and more rarely, by voluntary ingestion of cyanide salts. HCN is highly poisonous by all routes of administration. Its toxic effect involves inhibition of several metal-containing enzymes, the most critical of which is cytochrome C oxidase, an end-chain enzyme of cellular respiration. The cellular anoxia caused by cyanide administration primarily effects the cardiovascular, respiratory, and central nervous systems but many other organ systems may be involved in a poisoning event.

Phosgene Oxime

Phosgene oxime or CX is a potent chemical weapon from the group of vesicants or blister agents, specifically called an urticant or nettle agent. The compound has a strong, disagreeable odor and a violently irritating vapor. It induces *immediate* ocular, dermal, and respiratory damage resulting in casualties, reduction in fighting efficiency, and demoralization. In concentrations below 8%, it produces little biological damage. However, more concentrated dermal exposures produce lesions similar to those of mustard gas, with lesions extending into the muscle below. Inhalation exposure may cause immediately respiratory tract irritation, dyspnea, and leads to pulmonary edema. Edema may be accompanied by a necrotizing bronchiolitis and pulmonary venule thrombosis.[494]

Environmental Pollutants and Toxic Compounds

Dioxins

Dioxins are a broad group of chemicals that are persistent, lipophilic, and prone to build up in the food chain and bioaccumulation. The compound, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), is the most frequently studied of the group that also contains polychlorinated dibenzodioxins, polychlorinated dibenzofurans, and polychlorinated biphenyls (PCBs). In the modern world, the most common way that humans are exposed to dioxins are though ingestion of fatty foods such as meat (especially beef) and dairy products.[495,496] Other ways that people are exposed to dioxins are through occupational overexposure to herbicides, chemical pollutants in the environment, or by working in an industry that produces or uses dioxins. Many U.S. Vietnam War-era veterans (as well as many Southeast Asian veterans and civilians) were exposed to dioxins during the transport and spraying of Agent Orange herbicide. The potential health effects of the dioxin exposures experienced by U.S. veterans are discussed in the Military Health section of this report.

Arsenic

Inorganic arsenic is naturally present at high levels in the groundwater of a number of countries and contaminates drinking water, and crops irrigated or grown in the water (like rice). There is a strong body of evidence linking arsenic intake with a variety of health problems, from skin lesions and some cancers, to cardiovascular diseases, and metabolic disorders such as diabetes.[161,162] Organic arsenic can also be ingested from sources such as fish and shellfish, meat, and poultry, etc., but these arsenic compounds – such as arsenobetaine - are of low toxicity.[497]

Nitrogen Dioxide

Nitrogen dioxide (NO_2) is an atmospheric pollutant introduced into the environment by the fires of industry and combustion engines. Along with sulfur dioxide and other chemicals, it contributes significantly to smog in urban environments. It recent years there have been a number of studies linking NO_2 exposure to a wide variety of serious illnesses including cardiovascular and respiratory diseases, diabetes, and some cancers.

Propylene Glycol

The propylene glycols (PPGs) are a family of chemicals that are used industrially to produce polyester resins and are also used as humectants, solvents in many pharmaceuticals, and as preservatives in food. They are also one of the major ingredients in electronic cigarettes, the source of most current human exposures.

Acute propylene glycol toxicity sometimes occurs in hospital situations with continued intravenous infusion of medications and some antibiotics, because of the presence of PPGs in the intravenous solution.[347] Although this toxicity can have serious symptoms (significant hypotension, lactic acidosis, and decreased renal function), symptoms resolve when infusion is stopped, and exposure produces no long-term sequelae.[348]

Recent reviews and meta-analyses of the toxic effect of propylene glycols in electronic cigarettes is inconclusive about how harmful inhaled PPGs are.[349,350] Some studies report negative respiratory effects, such as mouth and throat irritation and the development of a dry cough, and other studies do not. To some degree, this variability of data is caused by methodological problems in the studies, including a lack of long-term follow-up of subjects. Additionally, some studies are sponsored by e-cigarette manufacturers.[351]

Barbiturates, Stimulants, & Antidepressants

Amobarbital

Amobarbital was once used as a sedative "truth serum" to coerce interrogation subjects to talk. It is now used for treatment of anxiety, epilepsy, and insomnia. Amobarbital is generally regarded as safe.

Phenobarbital

Phenobarbital is a barbiturate that works by increasing the activity of the inhibitory neurotransmitter GABA and is recommended by the World Health Organization for the treatment of certain types of epilepsy. In the developed world, it is commonly used to treat seizures in young children, but other medications are generally used by older children and adults.

MDMA (Ecstasy)

Over the past two decades, the amphetamine analog, "ecstasy," (3,4-methylene-dioxymethamphetamine, or MDMA) has become a popular recreational drug around the world. It induces feelings of euphoria, increases energy and sexual arousal, and suppresses the need to eat, drink, or sleep. Like other amphetamine-related drugs, MDMA acts indirectly, primarily by stimulating the release of monoamines, such as dopamine and serotonin (5-HT).

Iproniazid

Iproniazid was an MAO-inhibitor drug that was first labelled as an antidepressant in 1958, but was removed from major portions of the world market in 1961 because of its ability to induce hepatocellular injury and chronic hepatitis.

Miscellaneous Other Drugs and Diagnostic Substances

Phenazone

Phenazone is a non-steroidal anti-inflammatory drug used as an analgesic and antipyretic. It is a commonly used drug and generally regarded as safe. None of the databases consulted had recent publications linking it to toxicity, adverse effects, or sequelae.

Indocyanine green

Indocyanine green (ICG) is a cyanine dye used in medical diagnostics. It is also commonly used to improve the visualization of preretinal tissues during repair of macular holes or chromovitrectomy.

Aminohippuric acid (PAH)

Aminohippuric acid (PAH) is a diagnostic agent useful in medical tests involving the measurement of renal plasma flow. It is generally regarded as safe.

Bromsulphthalein (BSP)

Bromsulphthalein (BSP) is a dye used in liver function tests. It is generally regarded as safe. BSP is a commonly used contrast dye that is safe.

Miscellaneous Other Compounds

PABA

Para-aminobenzoic acid (PABA) was widely used as a sunscreen ingredient until the 1980s when it was recognized as a leading cause of sunscreen photoallergy. Concerns about its allergic and photoallergic potential led to a general reduction in its use. However, PABA is still used in Chinese cosmetic products and can also still be found in some sunscreens marketed in Europe.

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Nothing was found in any date range using any search strings.

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Nothing was found in any date range using any identifiers.

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Tox: B008 (Benzetimide HCl)

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Nothing was found using any search strings.

Tox: B011 (N-methyl-4-piperidyl cyclopentylmethyl-ethynylglycollate, PCMG)

Several older publications were found from the 1960s and 1970s, but there was nothing that was published within the date range for the search.

Tox: B012 (cis-2-Methyl-3-quinuclidinyl cyclopentylphenyl-glycolate)

No publications were found using any of the identifiers.

Tox: B013 (1-Methyl-4-piperidyl phenyl-(3-methylbut-1-yn-3-enyl)-glycolate)

Nothing found within the date limitations of the project

Tox: B014 (3-Quinuclidinyl (1-hydroxycyclopentyl) phenylacetate)

Searches with all of the identifiers only turned up the 2009 review by Mark Brown.

Tox B015 (3-Quinuclidinyl cyclopentyl-(2 –propenyl)-glycolate)

Nothing found.

Tox: B016 (4-(1-methyl-1,2,3,6-tetrahydropyridyl)-Methyl-Isopropylphenylglycolate)

Nothing useful was recovered.

Tox B018 (Benactyzine HCL (Amizil, Suvatil, Parasan, Nutinal)

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Tox: B023 (N-Methyl-4-piperidyl isopropylphenyl-glycolate)

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Tox: B025 (Toxogonin Atropine Benactyzine (TAB))

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Miscellaneous Drugs and Diagnostic Substances

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None of the databases consulted had recent publications linking phenazone to toxicity, adverse effects, or sequelae.

Indocyanine green

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Bromsulphthalein (BSP)

No publications were found that discussed toxicity, adverse reactions of long-term sequelae.

Miscellaneous Other Compounds

PABA (Para-aminobenzoic acid)

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12202

No references could be found for this compound.

Pyridine

No recent references were found for this compound.

CS Arsenic

No information on CS Arsenic was found.

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Octylamine

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Chloropicrin

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