Department of Defense/Veterans Affairs Deployment Health Work Group
Guidance for the Long-Term Follow-up of Service Members and Veterans Exposed to Chemical Warfare Agents during their Military Service in Iraq between 2003 and 2011

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1 REFERENCES

Appendix A provides the references cited within this document.

2 PURPOSE

The purpose of this document is to provide guidance for long-term follow-up and patient education to healthcare providers caring for Service members and Veterans exposed to chemical warfare agents (CWA) (sulfur mustard—a blister agent and sarin—a nerve agent) during military deployment to Iraq, as part of Operation Iraqi Freedom and/or Operation New Dawn (OIF/OND), between 2003 and 2011. For purposes of this document, there are no differences between branches of military service, or components, as long as the exposure occurred while the Service member was on Active Duty Federal status. These recommendations do not include guidelines for clinical treatment; existing clinical practice guidelines for specific exposures and health conditions should be followed. Appendix B provides a link to the Multi-Service Tactics, Techniques, and Procedures for Treatment of CWA Casualties and Conventional Military Chemical Injuries and provides sources of information regarding exposures to other substances.

3 BACKGROUND

These guidelines were developed for Service members and Veterans who had a symptomatic exposure to CWA during their military deployment to Iraq, in support of OIF/OND between 2003 and 2011. This proposed guidance presupposes that an exposed individual received a thorough medical evaluation to assess and document recovery/recuperation/residuals from any and all acute and sub-acute effects from the exposure. Examples include—

- An individual who had a clinically significant acute symptomatic inhalation exposure to sulfur mustard received an examination that included baseline pulmonary evaluation (e.g., high-resolution computerized tomography (HRCT) scan; pulmonary function test (PFT)) at baseline; and
- An individual with a sarin-related seizure or status epilepticus received a neurological evaluation with electroencephalogram.

Any medical evaluation that results in assessment and documentation as described above is sufficient. Examples include: examinations conducted in 2015 and 2016, as part of the CWA Initiative, fitness-for-duty examinations, job category-specific examinations, Release from Active Duty/separation/retirement/medical board examinations, and Veterans Administration (VA) vesting or registry examinations.
This document provides guidance for care of Service members and Veterans who have recovered from any and all acute and sub-acute effects from CWA exposure, regardless of the intensity of exposure. This guidance does not provide recommendations for acute or sub-acute treatment of CWA exposures. Some Service members, who had high levels of exposure resulting in the need for immediate, intensive, and often life-saving medical care, may have significant health problems related to their CWA exposure that persist indefinitely. These individuals should remain under the care and follow-up of the appropriate medical specialists as indicated by the ongoing CWA exposure-related health problems. Therefore, this document may never be applicable to these individuals. For more information and more in-depth discussion of these Veterans' health issues, please see “Veterans at Risk” (see Appendix B; Pechua, 1993).

This document represents the consensus of Department of Defense (DOD), VA, and non-governmental subject matter experts as of November 2015. Strength of the evidence is based on whether there exist several competently designed and executed studies with consistent, statistically significant outcomes (good); only one or two small flawed studies, without consistent statistically significant outcomes (poor); or somewhere in between (fair).

4 RECOMMENDED FOLLOW-UP PROCESS

- Provide all individuals who undergo evaluation for symptomatic CWA exposures with educational materials as discussed below.

- Review specific follow-up recommendations resulting from clinical evaluations with the individual, using principles of shared decision making; document the discussion in their DOD and/or VA medical record.

- Send a periodic follow-up letter or health status questionnaire to all individuals with a symptomatic exposure to CWA. The DOD and VA should coordinate on this matter. The purpose is threefold—
  (1) To provide patient education and updates with new information when available;
  (2) To help ensure optimal treatment of identified health conditions; and
  (3) To reassure the patient and demonstrate DOD/VA commitment to managing the health effects of CWA.

- Recommended follow-up should continue until it is terminated at the individual's request; an individual cannot be contacted after reasonable efforts; the individual's health conditions make continued follow-up unreasonable; or other information or research arises which precludes any value to continuing.
5 SULFUR MUSTARD EXPOSURE

5.1 Ocular Exposure

5.1.1 Summary of the Evidence

Individuals with significant ocular exposure to sulfur mustard (defined as those who required medical care, including ophthalmologic care for keratopathy for 8 weeks or greater, beginning at the time of the exposure) are believed to be at higher risk of delayed keratopathy\(^1\). This may occur at any time up to several decades after the exposure\(^2\). **[Note: There are no known cases of this level of eye exposure occurring in a combat zone among U.S. military personnel since World War (WW) II.]** Long-term risk has not been associated with mild exposure, which resulted in tearing, itching and a gritty sensation, burning/mild reddening of the eyes, or mild eye pain.

5.1.2 Strength of the Evidence

Good for those with significant exposure. Fair for those with minimal exposure.

5.1.3 Recommendations

- Stress the importance of good eye hygiene and eye care (e.g., avoid putting anything in the eyes that was not designed specifically for that use; see an eye care professional regularly.).

- Educate all individuals who required 8 weeks or more of medical care at the time of exposure about the possibility of recurrent keratopathy; encourage such individuals to see an eye care professional immediately in the event of otherwise unexplained eye pain or visual changes at any time after the exposure.

- Counsel all individuals with sulfur mustard ocular exposure to notify their eye care professionals and other healthcare providers about their exposure history.

- Encourage all individuals with sulfur mustard ocular exposure to report all diagnoses of keratopathy to their DOD or VA healthcare provider, as well as their Civilian healthcare provider (if applicable) so the information may be entered into their medical record(s).

- Recommend no formal DOD or VA medical surveillance. Late onset or late-occurring sulfur mustard exposure ocular effects [these are effects which were not present acutely or sub-acutely after the exposure] are impossible to predict and are unlikely to be identified in a periodic evaluation. Fortunately, late onset ocular effects are unlikely to occur based on the currently known level of exposure to U.S. military personnel.
5.2 Inhalation Exposure

5.2.1 Summary of the Evidence

Individuals who had clinically significant lung exposure to sulfur mustard have a high incidence of long-term pulmonary effects even several decades after their exposure. This includes individuals who developed inflammation of the upper and lower airways, tissue death of the airway lining, obstruction of the upper and/or lower airways, and secondary infection (pneumonia). These individuals typically had high or intermediate levels of exposure and required intensive or moderate immediate medical care at the time of the exposure; they were hospitalized as inpatients and often required this intensive medical care to prevent death. [Note: There have been no documented cases of high-level exposures to sulfur mustard involving U. S. Service members in a combat zone since WWII.]

Mild exposure symptoms include: runny nose, sneezing, nosebleed, hoarseness progressing to "toneless" voice, barking cough, loss of taste and smell, wheezing and difficulty breathing or shortness of breath in smokers and asthmatics, as well as nasal and sinus pain (occurring later). One study in the literature looked specifically at individuals 15 years post-exposure to sulfur mustard; these individuals reported having absolutely no symptoms at the time of exposure but indicated that they had symptoms at the time of the study. This study found several abnormalities on diagnostic testing of some of these individuals. There are several significant flaws in the study design, however, that limit the health significance of these abnormalities, including a lack of correlation between abnormal findings and number of exposure episodes; in addition, no corroborating studies could be located.

5.2.2 Strength of the Evidence

Good for those with clinically significant exposure. Poor for those with minimal exposure.

5.2.3 Recommendations

- Educate all individuals with suspected or reported sulfur mustard inhalation exposure about the possibility of long-term pulmonary effects and the importance of avoiding pulmonary toxins, including tobacco smoke and second-hand smoke.

- Educate all individuals about the importance of establishing and maintaining a close, ongoing relationship with a primary care practitioner who can recognize and respond to changes in clinical status. All individuals should report changes in their lung health to their provider.

- Encourage all individuals with symptomatic sulfur mustard inhalation exposure to report all cases of pulmonary symptoms and/or pulmonary diagnoses to their DOD or VA healthcare provider, as well as their Civilian healthcare provider (if applicable) to ensure that the information is entered into their medical record(s).
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- Encourage all individuals with minimally symptomatic or asymptomatic inhalation sulfur mustard exposure, who subsequently develop pulmonary symptoms beyond 48 hours post-exposure, to seek medical evaluation from their usual source of health care.

- Use each encounter for pulmonary evaluation as an opportunity to emphasize the importance of avoiding pulmonary toxins, most notably tobacco smoke.

5.3 Dermal Exposure

5.3.1 Summary of the Evidence

Individuals with clinically significant sulfur mustard dermal exposure may have long-term dermal effects, but there is no clear scientific or medical evidence of any risk for late-onset skin effects (i.e., effects which were not present acutely or sub-acutely after the exposure). Clinically significant sulfur mustard dermal exposure requires medical attention at the time of the exposure and often results in persistent scarring. Hyper- or hypo-pigmentation at the site may occur, and there are some rare reports of psoriasis developing. Sites previously injured by exposure may be more easily injured by direct trauma even after apparent healing. There are reports of cicatricial malignancies (developing in chronic scarring) from severe burns resulting from sulfur mustard exposure, although it is unclear whether this occurs at the same or higher rate than in scars from other causes of burns. There is no indication from the literature that individuals who remain asymptomatic for greater than 48 hours post-exposure are at any risk of subsequent dermatologic effects.

5.3.2 Strength of the Evidence

Good for those with clinically significant exposure. Good for those with minimal exposure.

5.3.3 Recommendations

- Educate all individuals with symptomatic sulfur mustard dermal exposure about the possibility of long-term dermal effects and the importance of avoiding subsequent dermal injuries to the affected skin, including sun and tanning booth-induced injuries.

- Educate all individuals with symptomatic sulfur mustard dermal exposure with residual scarring at the exposure site(s) about the possibility of cicatricial malignancies and the importance of seeing a skin care professional if the scar(s) begins to change color, shape, or texture. Encourage these individuals to report all diagnoses of cicatricial malignancies in sulfur mustard exposure-related scars to their DOD or VA healthcare provider, as well as their Civilian healthcare provider (if applicable), so the information may be entered into their medical record(s).

- Reassure all individuals with asymptomatic sulfur mustard dermal exposure that there is no evidence of long-term health effects in the absence of acute effects. Educate individuals about the importance of avoiding dermal trauma, including sun and tanning booth injuries.
5.4 Systemic Exposure

5.4.1 Summary of the Evidence

There is limited literature regarding systemic effects of sulfur mustard exposure. Sulfur mustard is incompletely absorbed (only about 8%) into the systemic circulation, but the possibility of systemic effects does exist. Sulfur mustard exposures resulting in burns to greater than 36% of the body surface area, ocular lesions, or forced expiratory volume in 1 second [FEV1] or forced vital capacity [FVC] less than 50% (both of these on pulmonary function testing) have been reported to be severe enough to cause fatal bone marrow suppression. This bone marrow suppression, and consequent marked reductions in white blood cells, occurs over several days prior to death. With non-fatal, high-level systemic sulfur mustard exposures, both T- and B-cell status and antibody levels may be acutely depressed but typically return to normal within several years. Natural killer-cell reductions have been described up to 2 decades after sulfur mustard exposure in individuals who had severe initial responses\(^1\). \[\text{Note: There have been no documented cases of high-level exposures to sulfur mustard involving U. S. Service members in a combat zone since WWII.}\]

5.4.2 Strength of the Evidence

Good for those with severe initial responses to their sulfur mustard exposure. Good for those with minimal exposure.

5.4.3 Recommendation

Recommend no formal DOD or VA medical surveillance. Sulfur mustard exposure systemic effects are unlikely to occur based on the levels of exposure during exposure incidents involving the United States.

6 NERVE AGENT EXPOSURE

Much is known about the acute and long-term health effects of nerve agent exposure at sufficiently high levels that the exposed individual would require immediate medical attention to avoid death. Less is known about exposures of lesser magnitude, although the literature to date seems consistent that there is minimal health impact to these exposed individuals. For purposes of this guidance, nerve agent estimated exposure for any individual will be based on initial acute signs and symptoms.

- High exposure: frank effects of cholinergic poisoning (convulsions, near lethality, or requiring intervention to prevent death);
Intermediate exposure: presence of threshold cholinergic effects (miosis, rhinorrhea, measurable depression of cholinesterase);

Low exposure: the absence of all but minimal immediate clinical signs and symptoms.

There is no credible scientific data supporting the development of late-onset symptoms (symptoms which were not present acutely or sub-acutely after the exposure) in a nerve agent-exposed person after the acute effects of nerve agent exposure have resolved.

6.1 High Exposure Level/Severe Exposure

6.1.1 Summary of the Evidence

These individuals typically required intensive medical care at the time of their exposures. Individuals whose red blood cell (RBC) cholinesterase activity was measured at the time of the exposure and found to be substantially lower than their baseline, will typically have normal values within 3–4 months. Once normalized, these values remain normal, and there is no value to repeat testing years later.

There is some evidence that after high-level nerve agent exposure, there may be long-term abnormalities on formal neuropsychological testing, as well as abnormalities on vestibular (balance) and vision testing, even in individuals that are asymptomatic at the time of testing. The importance of these test abnormalities is questionable, especially in individuals with no symptoms at the time of the testing. One study of victims of the Tokyo Subway Sarin Attack, conducted 5–6 years after the incident, identified gray and white matter brain volume changes. These changes correlated with significantly reduced cholinesterase levels measured at the time of the attack and also with non-specific (somatic) symptoms at the time of the study. There are no human studies demonstrating the development of late-onset symptoms from confirmed nerve agent exposure. That is, if there were no symptoms at the time of exposure, there is no evidence that symptoms will develop later.

6.1.2 Strength of the Evidence

Good. Some findings of questionable clinical significance.

6.1.3 Recommendations

- All individuals with high-level exposure to nerve agents should undergo comprehensive neurological evaluation (with consideration of neuropsychological, vestibular, and ophthalmologic testing and/or referrals) to determine if there are any residual effects from their exposures. This applies to highly exposed individuals whether or not they are symptomatic at the time of their initial referral for specialty evaluation (see paragraph 6.1.1). This/these evaluation(s) should attempt to isolate any residual nerve-agent-exposure effects from any effects due to Post-Traumatic Stress Disorder (PTSD) and/or Traumatic Brain Injury (TBI). If this evaluation and concurrent testing are normal, or if abnormal but explained by other factors (e.g.,
PTSD, TBI), no further follow-up is recommended. [Note: There have been no documented cases of high-level exposures to nerve agents involving U. S. Service members in a combat zone since these agents were developed in the 1930s.]

- If the above tests are abnormal and cannot be explained by a non-nerve agent-related condition or situation, refer the individual to a neurologist, neuropsychologist, otolaryngologist, or ophthalmologist (as appropriate) for further evaluation and follow-up.

- Once these tests normalize, or another cause for the abnormalities is identified, or the individual becomes asymptomatic with residual test abnormalities, no further follow-up is recommended.

6.2 Intermediate Exposure Level/Moderate Exposure

6.2.1 Summary of the Evidence

These individuals typically required some medical care at the time of their exposures but did not require intensive care or, in most cases, inpatient hospitalization. Signs and symptoms of moderate exposure are pinpoint pupils; runny nose; blurred vision; shortness of breath; abnormally excessive sweating, drooling, nausea, vomiting; and lower RBC cholinesterase level on blood testing. These can rapidly progress to muscle twitching and confusion.

As noted above, individuals with diminished RBC cholinesterase activity at the time of the exposure will typically have normalized the value within 3–4 months and do not require further testing years later.

There is some evidence that after intermediate level nerve-agent exposure, there may be long-term abnormalities on neuropsychological testing. There may also be abnormalities with balance and vision even in individuals asymptomatic at the time of testing (although these findings are of questionable clinical significance)\(^{(4,5)}\). As previously noted, there is a published study\(^{(6)}\) of victims of the Tokyo Subway Sarin Attack suggesting gray and white matter volume changes that correlated with significantly reduced cholinesterase levels at the time of the attack and with the level of somatic symptoms at the time of testing\(^{(6)}\). There are no human studies that demonstrate late-onset symptoms (symptoms that were not present acutely or sub-acutely after the exposure) from symptomatic nerve agent exposure.

6.2.2 Strength of the Evidence

Good. Some findings are of questionable clinical significance.

6.2.3 Recommendations

- All individuals with symptomatic, intermediate-level exposure to nerve agents (i.e., individuals that have sustained exposure requiring more than minimal medical
treatment at the time) should undergo comprehensive neurologic evaluation (with consideration of neuropsychological and vestibular testing) to determine if there are any residual effects from their exposures. This applies whether or not they are symptomatic at the time of their initial referral for specialty evaluation (see paragraph 6.2.1). This evaluation should attempt to isolate any residual nerve-agent exposure effects from any effects due to PTSD and/or TBI. If this evaluation and concurrent testing are normal or if abnormal, but explained by other factors, no further follow-up is recommended.

- If the above tests are abnormal and cannot be explained by a non-nerve agent-related condition or situation, it is recommended that the individual be referred to a neurologist, neuropsychologist, ophthalmologist, or otolaryngologist (as appropriate) for further evaluation and follow-up.

- Once these tests normalize, or another cause for the abnormalities is identified, or the individual becomes asymptomatic with residual test abnormalities, no further follow-up is recommended.

6.3 Mild or Low Exposure Level/Mild or Minimal Exposure

6.3.1 Summary of the Evidence

These individuals typically required minimal, if any, medical care at the time of their exposures or did not seek medical care at the time of their exposure. Mild to minimal exposure causes pinpoint pupils, with or without runny nose, nausea and vomiting, or may cause no symptoms at all. Mild symptoms such as pinpoint pupils resolve quickly. Those who experience mild, minimal, or no symptoms at the time of the exposure are not expected to develop new symptoms and should not develop any exposure-related health problems that affect their daily lives.

There is some literature that supports a statistically significant increase in asymptomatic long-term neuropsychological, neurological, or electrocardiographic abnormalities after low-level nerve agent exposure. When present, the clinical significance of these abnormalities, in these individuals, is not yet known. Therefore, testing for these changes should be confined to approved research protocols and at this time has no role in clinical assessments. There are no studies that support late-onset symptoms (symptoms that were not present acutely or sub-acutely after the exposure) after nerve agent exposure.

6.3.2 Strength of the Evidence

Good.

6.3.3 Recommendations

- All individuals with mild or low-level exposure to nerve agents should be educated regarding what is known about late-onset effects of nerve agent exposure, especially
in cases of mild or no symptoms at the time of the exposure. No follow-up is recommended.
APPENDIX A

REFERENCES AND DISCUSSION

   The author studied 84 individuals (ages 42-63 at time of study) with delayed mustard gas keratitis and a history of sulfur mustard exposure in 1917-1918 during World War I. The exposures took place 26 to 27 years earlier. Overall, the time to subsequent vision issues ranged from 12 to 21 years after the initial exposure. The study found that the corneal damage resulting from the initial injury heal but leave faceted scars which gradually diminish visual acuity. It was noted that no delayed keratitis was observed in cases where initial ocular effects lasted for less than 8 weeks.

   “In <1% of patients with battlefield exposure to SM, a delayed type of ulcerative keratopathy may develop, leading to late-onset blindness. The maximum incidence usually occurs 15–20 years after initial exposure, although latency periods as long as 40 years or as short as 6 years have also been reported. Frequency of delayed keratitis in our patients, who had been severely intoxicated and were at the peak incidence period in terms of years after exposure, were 15%. Except for this particularly ominous condition, other ocular effects of SM poisoning generally tend to decrease in time.”

   The authors looked specifically at individuals 15 years post-exposure to sulfur mustard who reported having no symptoms (including lacrimation, cough, red eyes, and so forth) at the time of exposure. These individuals were all symptomatic at the time of the study. Out of 77 people included in the study, 34 underwent HRCT and (PFT. There was no indication in the report how the 34 were selected from the 77. Out of this group of 34 individuals, 12 reported a single exposure episode, 14 had two exposures, and 8 were exposed for than twice. From this smaller cohort, abnormalities (at least air trapping) were identified on HRCT in 21 out of 34 cases and on PFT in 5 out of 34 cases. No correlation was provided between abnormal findings and the number of exposure episodes.

   At 6 months post exposure, 18 victims of the Tokyo Subway Sarin Attack (TSSA) were admitted to one of the treating hospitals underwent neurological evaluations. No clinical abnormalities were detected that could be attributed to sarin poisoning when compared to sex- and age-matched controls. Neurophysiological evaluations showed prolonged latency
of event-related and visual evoked potentials, and larger postural sway. Alterations in electrocardiogram (RR intervals) as an assessment of peripheral autonomic nervous system function was detected and correlated with the level of RBC-ChE decreases during the acute exposure phase.

5. Miyaki K, Nishiwaki Y, Maekawa K, et al. 2005. Effects of sarin on the nervous system of subway workers seven years after the Tokyo subway sarin attack. *J Occup Health* (Japan), 47:299-304. The authors assessed neurobehavioral and psychomotor function of 23 sarin-exposed subway workers 7 years after the TSSA. Five of the test subjects were characterized as having high exposure (hospitalized) while 18 were characterized as having low exposure (outpatient status). Their performance was compared to 13 age- and occupation-matched control subjects. Performance in one psychomotor test (finger tapping tests for both dominant and non-dominant hand) was significantly poorer than for the controls. This statistically significant difference was in all exposed and high exposed groups, but not in low exposed individuals. Performance in one of the memory tests (digital backward span test) was also deficient compared to controls. Other neurobehavioral tests and stabilometry did not show exposure-related changes.

6. Yamasue H, Abe O, Kasai K, et al. 2007. Human Brain Structural Change Related to Acute Single Exposure to Sarin. *Ann Neurol*, 2007;61:37–46. The authors performed magnetic resonance imaging (MRIs) and diffusion tensor MRI (DTI) on a cohort of 38 victims of the TSSA, 5-6 years after the attack. All of these victims required emergency department treatment immediately after their exposure in 1995; thus, the authors postulate that the victims were exposed at the intermediate or high level. The authors found a significant decrease in regional gray matter and white volumes in specific areas of the brain in victims of sarin exposure compared with matched control subjects. Regional white matter volume in one area showed a significant positive correlation with serum ChE levels at the time of the incident. Furthermore, reduced regional white volume in another area was significantly related to the severe, long-lasting somatic complaints of the victims.
APPENDIX B
OTHER SOURCES OF USEFUL INFORMATION

What Service Members and Veterans Should Know About Long-Term Effects of Exposure to Chemical Warfare Agents—Sarin.

What Service Members and Veterans Should Know About Long-Term Effects of Exposure to Chemical Warfare Agents—Sulfur Mustard.

http://books.nap.edu/openbook.php?isbn=030904832X

http://www.nap.edu/catalog/9953/gulf-war-and-health-volume-1-depleted-uranium-pyridostigmine-bromide

http://www.nap.edu/read/11064/chapter/1


http://www.atsdr.cdc.gov/mmg/Index.asp
ATSDR. Medical Management Guidelines for Blister Agents: Sulfur Mustard Agent H or HD \((\text{C}_4\text{H}_8\text{Cl}_2\text{S})\), Sulfur Mustard Agent HT. \url{http://www.atdsr.cdc.gov/mmg/mmg.asp?id=924&tid=191}

ATSDR. Medical Management Guidelines for Nerve Agents: Tabun (GA); Sarin (GB); Soman (GD); and VX. \url{http://www.atdsr.cdc.gov/mmg/mmg.asp?id=523&tid=93}

ATSDR. Medical Management Guidelines for Chlorine. \url{http://www.atdsr.cdc.gov/mmg/mmg.asp?id=198&tid=36}

ATSDR. Medical Management Guidelines for Ammonia. \url{http://www.atdsr.cdc.gov/mmg/mmg.asp?id=7&tid=2}


If you are a healthcare provider with questions regarding the above guidance, please contact the U.S. Army Public Health Center at usarmy.apg.medcom-phc.mbx.emp@mail.mil or call us at 410-436-2714.