INSTITUTE FOR DEFENSE ANALYSES

Analysis of Non-Acute, Sub-Lethal Chemical/ Biological Injuries and Illnesses, Part II

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January 2019
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IDA Paper P-10390
Log: H 18-000529

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About This Publication
This work was conducted by the Institute for Defense Analyses (IDA) under contract HQ0034-14-D-0001, project CA-6-4445, "The Medical CBRN Defense Planning & Preparedness Project," for the Joint Staff, Joint Requirements Office (JRO) for Chemical, Biological, Radiological and Nuclear (CBRN) Defense (J-8/JRO) and the U.S. Army Office of the Surgeon General (OTSG). The views, opinions, and findings should not be construed as representing the official position of either the Department of Defense or the sponsoring organization.

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Acknowledgments
The authors wish to acknowledge the technical reviews conducted by Dr. Mark Bohannon and Dr. Jon Davis, the assistance with tables and figures by Dr. Audrey Kelley, project leadership by Dr. Sean Oxford, document production assistance by Ms. Amberlee Mabe-Stanberry, and the careful editing by Mr. John C. Everett.

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Executive Summary

Most information on the effects from chemical and biological agents, including previous efforts by the Institute for Defense Analyses (IDA), has focused only on acute effects.* Long-term effects are not relevant on the battlefield, but could have significant consequences for the military and veteran medical systems and individuals' future health, ability to serve, and quality of life. Part I of this analysis† was a quick look at the potential long-term effects of 27 chemical and biological agents included in North Atlantic Treaty Organization (NATO) chemical, biological, radiological, and nuclear (CBRN) casualty estimation doctrine that IDA created. The information available in the literature for 17 agents was fully described in Part I, while 10 agents had too much information available in the literature to be fully described in that paper. This paper, Part II, describes fully the long-term effects of 10 agents: brucellosis, melioidosis, Q fever, nerve agents (tabun, sarin, soman, cyclosarin, and VX), sulfur mustard, and chlorine. The fuller literature review in Part II was especially useful for describing agents that can produce many different kinds of long-term effects (e.g., brucellosis or sulfur mustard) or that produce effects that are often overestimated in reviews (e.g., melioidosis or chlorine). "Long-term effects" were defined as effects that lasted for longer than 3 months after acute injury (or appeared after 3 months) and were the direct result of an acute exposure to the agent.

The long-term effects of biological agents were separated into five categories: "no effect," "mild effect," "relapse," "severe effect," and "not applicable (N/A)." The severity of the effect was somewhat subjective but was based on how debilitating the effect is. For example, chronic fatigue was listed as a mild effect but blindness was listed as a severe effect. "Not applicable" meant that there was either no information in the literature on long-term effects of that agent or the agent has a ~100% fatality rate. Table ES-1 shows the long-term effects of all 15 biological agents, based on Part I and Part II of IDA's analysis.

The long-term effects of chemical agents following mild/moderate or severe/very severe acute exposure were separated by organ system (neurological, respiratory, ocular, or skin). Table ES-2 shows the long-term effects of all 12 chemical agents based on Part I

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* Sean M. Oxford et al., "Technical Reference Manual to *Allied Medical Publication 7.5 (AMedP-7.5) NATO Planning Guide for the Estimation of CBRN Casualties*," IDA Document D-8122, (Alexandria, VA: Institute for Defense Analyses, October 2016).

† Kristen A. Bishop and Carl A. Curling, *Analysis of Non-Acute, Sub-Lethal Chemical/Biological Injuries and Illnesses*, IDA Paper P-8865, (Alexandria, VA: Institute for Defense Analyses, January 2018).

and Part II of IDA's analysis (the nerve agent class includes tabun, sarin, soman, cyclosarin, and VX). When combined, the descriptions of long-term effects from chemical and biological agents in Part I and Part II of this series provide a solid basis for understanding what to expect and look for from these agents in the months and years to come after the initial exposure.

Table ES-1. Effects of Biological Agents

Not Applicable	No Effect	Mild Effect	Relapse	Severe Effect
Anthrax (Un) – 100% fatality rate	Plague (Tr) – no effects found upon follow-up	Q fever (Un and Tr) – Chronic Fatigue Syndrome (CFS) in ~20% for years afterwards	Brucellosis (Un) – can produce relapsing illness for years	EEE (Un) – can have mild to severe neurological sequelae, secondary to encephalitis (33%)
Plague (Un) – 100% fatality rate	SEB (Un) – no effects found upon follow-up	VEE (Un) – rarely, can have slight hand tremor or weakness	Brucellosis (Tr) – relapse in 5%–15% of those treated with full antibiotic regimen	Botulism (Un and Tr) – after moderate or severe acute symptoms, can have weakness, difficulty speaking/ swallowing, and so forth. (~50%)
Ricin – no information	Tularemia (Tr) – no effects found upon follow-up	WEE (Un) – rarely, can have slight hand tremor or weakness	Glanders (Un and Tr) – relapse days to years after	Q fever (Un and Tr) – endocarditis/vascular infection (1%), almost always in those with previous valve/heart conditions
T-2 – no information		Tularemia (Un) – can last up to 15 months	Melioidosis (Un) – same as glanders	Brucellosis (Un and Tr) – localized infections (1%–7%) in heart or nervous system
		Brucellosis (Un) – can produce sustained illness for years	Melioidosis (Tr) – relapse in <5% of those treated with full antibiotic regimen	Smallpox (Un) – blindness in <1%
				Anthrax (Tr) – decreased lung function in >50%

Legend: Neurological | Acute Symptoms Last More than 3 Months | Relapse of Acute Symptoms | Localized Infection | Other

Note: EEE = Eastern Equine Encephalitis, SEB = Staphylococcal Enterotoxin B, VEE = Venezuelan Equine Encephalitis, WEE = Western Equine Encephalitis, Un = untreated, Tr = treated.

Table ES-2. Effects of Treated Chemical Agents

Exposure	Neurological	Respiratory	Ocular	Skin
Mild/Moderate Acute Exposure	Sarin – most recover completely, some have anxiety, depression, or memory problems after Tabun, soman, cyclosarin, VX – same as sarin	Sulfur mustard – chronic bronchitis and other lung effects in ~30%–50%, worsens over time Phosgene – some have difficulty breathing up to 3 years afterwards Chlorine – RADS in a few for up to 6 months	Sulfur mustard – ocular injuries in <10%	Sulfur mustard – mild effects, including skin lesions, dry skin, itching, and burning in ~40%
	Hydrogen sulfide – headache, balance in ~30%			
Severe/Very Severe Acute Exposure	Sarin – after seizures can have brain damage Tabun, soman, cyclosarin, VX – same as sarin	Sulfur mustard – chronic bronchitis and other lung effects in ~30%–50%, worsens over time Ammonia – smokers especially have difficulty breathing up to 10 years afterwards Phosgene – some have difficulty breathing up to 3 years afterwards Chlorine – RADS in ~30% for up to 6 months	Sulfur mustard – ocular injuries and/or corneal scarring in ~10% Ammonia – blindness after spraying eyes	Sulfur mustard – mild effects, including skin lesions, dry skin, itching, and burning in ~40%
	Hydrogen sulfide – severe neurological sequelae from anoxic brain damage in ~30%–50% Hydrogen cyanide – ~40% neurological sequelae from anoxic brain damage Cyanogen chloride – same as hydrogen cyanide			

Legend: Severe Effects from Seizures | Severe Effects from Anoxia | Sulfur Mustard | Irritant Gases

Note: RADS = Reactive Airways Dysfunction Syndrome.

Contents

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1. Introduction

A. Summary of Part I

This paper is the second of a two-part series on the long-term effects of chemical and biological agents. The first paper in the series is referred to here as Part I.[1] In total, the long-term effects of 27 agents have been summarized in the two papers. The list of agents was taken from *NATO Allied Medical Publication 7.5 (AMedP 7.5)*, which is a planning guidance for the estimation of chemical, biological, radiological, and nuclear (CBRN) casualties.[2] The agents discussed in *AMedP-7.5* include most of the traditional biological and chemical agents.

Part I was a quick-look analysis of the long-term effects of the 27 agents. Of these 27 agents, all but 4 agents had at least one report of long-term effects following exposure. Two of the four had no information on these long-term effects, and the other two found upon follow-up that all the people exposed to those agents recovered fully. Because Part I was a quick-look analysis, it concentrated on agents for which there was not enough information in the literature to be able to complete the full analysis of long-term effects. Ten agents had too much information in the literature to be fully analyzed in Part I. Table 1 gives a list of agents categorized by amount of data available.

The long-term effects of the 10 agents that could not be fully described in Part I (see the last column of Table 1) are described in this paper. The nerve agent class includes five agents: tabun, sarin, soman, cyclosarin, and VX. These 10 agents were integrated into the classification of agents by type of effect used in Part I. The Executive Summary and the Chapter 4 of this paper include the conclusions from Part I and Part II.

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1 Kristen A. Bishop and Carl A. Curling, *Analysis of Non-Acute, Sub-Lethal Chemical/Biological Injuries and Illnesses*, IDA Paper P-8865 (Alexandria, VA: Institute for Defense Analyses, January 2018).

2 Sean M. Oxford, *NATO Allied Medical Publication 7.5 (AMedP-7.5) NATO Planning Guide for the Estimation of CBRN Casualties: Edition A, Version 1, Final Draft*, IDA Document NS D-8181 (Alexandria, VA: Institute for Defense Analyses, December 2016).

Table 1. Amount of Data Found for Biological and Chemical Agents

No Data	Little Data	More Data
Ricin	Anthrax	Brucellosis
T-2 mycotoxin	Glanders	Melioidosis
	Plague	Q Fever
	Tularemia	Nerve agents
	Smallpox	Sulfur mustard
	Encephalitides	Chlorine
	Botulism	
	Staphylococcal enterotoxin B (SEB)	
	Phosgene	
	Ammonia	
	Hydrogen cyanide	
	Cyanogen chloride	
	Hydrogen sulfide	

Note: Encephalitides includes Eastern Equine Encephalitis (EEE), Venezuelan Equine Encephalitis (VEE), and Western Equine Encephalitis (WEE). Nerve agents include tabun, sarin, soman, cyclosarin, and VX.

B. Scope and Methods

The scope and methods of this paper are almost identical to Part I, except that all 10 agents in this paper are described in full.[3] Both papers describe only the long-term effects from acute exposures. They do not include effects from chronic, long-term exposures unless those effects could provide additional evidence for a condition observed after acute exposure. The time period used to distinguish "long-term effects" or sequelae from acute effects was 3 months. The timing was somewhat arbitrary, but virtually all effects that lasted at least 3 months did not resolve for months or years—if ever—after that.

The analysis assumes that the individuals exposed to the agent/disease would be within the military population. Therefore, effects only seen in children or the infirm (before exposure) are excluded. "Adults" were considered to be the population above 10 years of age since not all papers gave exact ages, and "the infirm" were assumed to be those who would be excluded from the military due to preexisting medical conditions such as major heart defects. All countermeasures are assumed to be taken in accordance with prescriptions. Relapses following improper antibiotic use, for example, are not included. Only the long-term effects from the agents listed in *AMedP-7.5* are analyzed, and chemicals or diseases that are similar, such as organophosphate (OP) insecticides, are not discussed.

[3] Bishop and Curling, *Analysis of Non-Acute, Sub-Lethal Chemical/Biological Injuries and Illnesses*, 3-5.

The psychological effects arising from a terrorist attack or accident, as opposed to the psychological effects resulting directly from the agent or disease's pathology, were not included in this analysis. It is anticipated, for example, that civilians subjected to a chemical or biological attack, such as those affected in the Tokyo subway attack or the Iran-Iraq War, would have high levels of distress not necessarily related to specific symptoms of sarin or sulfur mustard. For some agents, such as nerve agents, it is difficult to separate the two, but caveats are given when appropriate.

The literature review performed for this analysis primarily looked at case studies, epidemiology studies, and some experimental results. The instances described in these reports occur from accidental, intentional, or natural exposures. Information on the long-term effects of biological agents usually comes from natural exposures, and information on the long-term effects of chemical agents usually comes from accidental and intentional exposures. Chemical agents, therefore, are often described in case reports or reports from large numbers of people exposed in a specific incident (e.g., the Tokyo sarin attack).

No date restrictions were placed on the papers or reports examined. The papers reviewed in the creation of *AMedP-7.5* were reviewed again for this paper, and a Google scholar search was performed for additional articles. The search terms included "agent long-term" or "agent sequelae." If specific sequelae were known to occur from the agent (endocarditis, relapses, and so forth), we also searched for that sequelae plus the agent name. Only the first 100 articles found in the Google scholar search were included since these articles typically contained the most useful results. Relevant references were taken from papers found in the initial searches. Papers that did not include follow-up with patients or papers written in foreign languages were not reviewed.

Many reports of exposure to chemical agents do not include the acute dose. For these agents, the acute dose was estimated from acute symptoms, using the symptoms severity metric in *AMedP-7.5*.[4] Mild symptoms are those that may not affect the ability to conduct a mission and can usually be treated by the individuals themselves. Moderate symptoms usually require medical care but typically on an outpatient basis. Severe symptoms are not life-threatening but usually require hospital care. Very severe symptoms imminently endanger life and can result in death without immediate medical intervention.[5]

Chapter 2 describes the long-term effects of three biological agents not fully reviewed in Part I: brucellosis, melioidosis, and Q fever. Chapter 3 describes the long-term effects of seven chemical agents not fully reviewed in Part I: tabun, sarin, soman, cyclosarin, and VX (these five agents are combined into the category "nerve agents"), sulfur mustard, and

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4 Sean M. Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5) NATO Planning Guide for the Estimation of CBRN Casualties*, IDA Document D-8122 (Alexandria, VA: Institute for Defense Analyses, October 2016), 2-4.

5 Ibid.

chlorine. A box with the conclusions on long-term effects is found at the end of each section (the long-term effects of nerve agents are combined). Chapter 4 provides the conclusions from Parts I and II of the analysis.

2. Long-Term Effects of Biological Agents

Information on the long-term effects of biological agents typically comes from natural outbreaks. Part I of this analysis described the long-term effects of 12 biological agents in full, but 3 agents had too much information available in the literature to be able to finish the full analysis within a quick-look review.[6] This paper (Part II) completes the literature review of three agents: brucellosis, melioidosis, and Q fever. In addition to the concluded long-term effects from each agent, appropriate caveats to the study and gaps in the literature are also presented.

A. Brucellosis

Brucellosis is caused by bacteria in the genus *Brucella.* When untreated, brucellosis can be a prolonged illness and is generally separated into three types based on duration: acute (<8 weeks), sub-acute (8–52 weeks), and chronic (>52 weeks).[7] Acute symptoms include fever, sweats, chills, headache, malaise, fatigue, weight loss, arthralgia, and myalgia.[8]

The duration of untreated brucellosis is generally determined from case reports and reviews published before the dawn of antibiotics and standard treatments. Table 2 gives a list of the durations reported in each of these cases. As shown, the illness lasted between 2 weeks and 4 months. Basset-Smith, however, suggested that untreated brucellosis can last 2 years or more.[9] This finding is more in line with information from recent studies. Chronic brucellosis can manifest in many ways, but one of the most common forms in untreated patients is a relapse/remission cycle of fever and associated symptoms.[10] Simpson found that of 90 brucellosis patients, 11 had a relapse and remission, while the

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6 Bishop and Curling, *Analysis of Non-Acute, Sub-Lethal Chemical/Biological Injuries and Illnesses*.

7 B. Aygen et al., "Clinical Manifestations, Complications and Treatment of Brucellosis: A Retrospective Evaluation of 480 Patients," *Médicine et Maladies Infectieuses* 32, no. 9 (September 2002): 485–493, https://doi.org/10.1016/S0399-077X(02)00403-1.

8 Oxford et al., "Technical Reference Manual to *Allied Medical Publication 7.5 (AMedP-7.5)*, 20-16–20-20.

9 P. W. Bassett-Smith, "Mediterranean or Undulant Fever," *British Medical Journal* 2, no. 3228 (November 11, 1922): 902–905, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2417002/.

10 Ibid.

Table 2. Duration of Untreated Brucellosis

Patient Number	Patient Age	Duration	Notes	Source
1	33	4–5 months		Gilbert (1928)[11]
2	20	2 weeks		Gilbert (1928)
3	26	4 months		Gilbert (1928)
4	20	10 weeks	At 10 months, still easily fatigued	Gilbert (1928)
5	47	2 months		Gilbert (1928)
6	30	3 months		Gilbert (1928)
7	30	3–4 weeks		Gilbert (1928)
8	28	5 weeks		Gilbert (1928)
9	56	3.5 months		Gilbert (1928)
10	25	11 weeks		Atwood (1930)[12]
11	42	11 weeks		Atwood (1930)
12	56	8 weeks		Atwood (1930)
13	38	11 weeks		Atwood (1930)
14	20	20 weeks		Atwood (1930)
15	14	8 weeks		Atwood (1930)
16	40	4 weeks		Atwood (1930)
17	34	8 weeks		Atwood (1930)
18	42	11 weeks		Atwood (1930)
19	16	16 weeks		Shera (1931)[13]
20	45	9 weeks		Shera (1931)
21	10	9 weeks	Followed by a slow but successful convalescence	Shera (1931)
22	25	7 weeks		Shera (1931)

Note: Many of these durations are also listed in Oxford et al., "Technical Reference Manual to *Allied Medical Publication 7.5 (AMedP-7.5)*, 20-21–20-23.

[11] Ruth Gilbert and Marion B. Coleman, "Recent Cases of Undulant Fever in New York State," *The Journal of Infectious Diseases* 43, no. 4 (Oct. 1928): 273–277, https://www.jstor.org/stable/30083541.

[12] George E. Atwood and H. E. Hasseltine, "Undulant Fever in Ware County, GA," *Public Health Reports* 45, no. 24 (June 13, 1930): 1343–1354, https://www.jstor.org/stable/4579681.

[13] A. Geoffrey Shera, "Four Cases of Undulant Fever," *The British Medical Journal* 2, no. 3691 (Oct. 3, 1931): 605–607, https://www.jstor.org/stable/25340853?seq=1#metadata_info_tab_contents.

rest had a single febrile episode.[14] Other symptoms of untreated chronic brucellosis include a single febrile episode that lasts longer than a year, localized infections, or mild chronic symptoms of depression, sexual impotence, tiredness, and aches and pains.[15]

Since brucellosis can be an insidious disease, many people can have it for long periods before seeking medical treatment. This situation is especially true in many of the Middle Eastern countries where brucellosis is endemic. Table 3 shows the time that patients had symptoms before they came to a hospital to begin treatment of brucellosis. Most papers separated brucellosis cases into acute, sub-acute, and chronic based on the time it took for patients to present. Patients with acute brucellosis (approximately 60%–70% of cases) presented within 8 weeks after the beginning of symptoms. Patients with sub-acute brucellosis (approximately 12%–30% of cases) presented between 8 and 52 weeks after the beginning of symptoms. Patients with chronic brucellosis (approximately 5%–15% of cases) presented more than 52 weeks after the beginning of symptoms. The symptom profile for those who initially present with acute, sub-acute, or chronic brucellosis is typically identical. In a study of 400 brucellosis patients in Kuwait, the only symptom profile differences were a higher rate of myalgia and arthritis among patients with sub-acute brucellosis and a higher rate (although still low) of constipation, insomnia, depression, and anxiety in those with sub-acute or chronic brucellosis.[16] The rate of people arriving at the hospital after more than 12 months of illness suggests, along with some of the cases from before antibiotics, that untreated brucellosis can last longer than a year in many instances.

Localized infection occurs frequently in brucellosis, with localization in bones or joints the most common.[17] Untreated localized infections can last for decades. One man had brucellar infection of his knee for 20 years.[18] Prostheses are also common locations for

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14 Walter M. Simpson, "Undulant Fever (Brucelliasis): A Clinico-Pathologio Study of Ninety Cases Occurring in and about Dayton, Ohio," *Annals of Internal Medicine* 4, no. 3 (September 1930): 238–259, http://annals.org/aim/article-abstract/669557/undulant-fever-brucelliasis-clinicopathologio-study-ninety-cases-ocurring-about-dayton.

15 Leighton E. Cluff, Robert W. Trever, and John B. Imboden, "Brucellosis II: Medical Aspects of Delayed Convalescence," *AMA Archives of Internal Medicine* 103, no. 3 (March 1959): 398–405, doi:10.1001/archinte.1959.00270030054005.

16 A. R. Lulu et al., "Human Brucellosis in Kuwait: A Prospective Study of 400 Cases," *Quarterly Journal of Medicine* 66, no. 249 (January 1988): 39–54, https://www.ncbi.nlm.nih.gov/pubmed/3051080.

17 J. D. Colmenero et al., "Complications Associated with *Brucella melitensis* Infection: A Study of 530 Cases," *Medicine* 75, no. 4 (July 1996): 195–211, https://www.ncbi.nlm.nih.gov/pubmed/8699960.

18 Huseyin Yorgancigil, Guler Yayli, and Orhan Oyar, "Neglected Case of Osteoarticular *Brucella* Infection of the Knee," *Croatian Medical Journal* 44, no. 6 (December 2003): 761–763, https://www.ncbi.nlm.nih.gov/pubmed/14652892.

Table 3. Rates of Chronic Brucellosis upon Initial Presentation at Hospital

Location	Total # Patients	# Acute (<8 weeks)	# Sub-Acute (8–52 weeks)	# Chronic (>52 weeks)	# Endo-carditis	# Neuro-brucellosis	Source
Kuwait	400	308 (77.0%)	50 (12.5%)	42 (10.5%)	8 (2.0%)	29 (7.3%)	Lulu (1988)[19]
Spain	530	475 (83.7%)	55 (16.3%)[a]	Unknown	6 (1.1%)	9 (1.7%)	Colmenero (1996)[20]
Turkey	467	322 (69.0%)	121 (25.9%)	24 (5.1%)	2 (0.4%)	31 (6.6%)	Aygen (2002)[21]
Iran	469	255 (54.4%)	179 (38.2%)	35 (7.4%)	3 (0.6%)	3 (0.6%)	Roushan (2004)[22]
Turkey	216	Unknown	Unknown	Unknown	5 (2.3%)	9 (4.2%)	Ertek (2006)[23]
Turkey	995	633 (63.6%)	222 (22.3%)	140 (14.1%)	7 (0.7%)	58 (5.8%)	Buzgan (2010)[24]

[a] Symptom durations in Colmenero (1996) were only separated into those who had symptoms for more than 3 months and those who had symptoms for less than 3 months. These durations are listed as acute and sub-acute illnesses in this table.

[19] Lulu et al., "Human Brucellosis in Kuwait."

[20] Colmenero et al., "Complications Associated with *Brucella melitensis* Infection."

[21] Aygen et al., "Clinical Manifestations, Complications and Treatment of Brucellosis."

[22] M. R. Hasanjani Roushan et al., "Epidemiological Features and Clinical Manifestations in 469 Adult Patients with Brucellosis in Babol, Northern Iran," *Epidemiology and Infection* 132, no. 6 (December 2004): 1109–1114, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2870202/.

[23] Mustafa Ertek et al., "Complications of *Brucella* Infection among Adults: An 18-Year Retrospective Evaluation," *Turkish Journal of Medical Sciences* 36, no. 6 (January 2006): 377–381, http://journals.tubitak.gov.tr/medical/issues/sag-06-36-6/sag-36-6-10-0508-7.pdf.

[24] Turan Buzgan et al., "Clinical Manifestations and Complications in 1028 Cases of Brucellosis: A Retrospective Evaluation and Review of the Literature," *International Journal of Infectious Diseases* 14, no. 6 (June 2010): e469–e478, https://doi.org/10.1016/j.ijid.2009.06.031.

brucellar infection.[25] Most localized infections, however, go away with antibiotic therapy and have no sequelae. The two categories of localized infections that are rare but can produce long illnesses or sequelae are endocarditis and neurobrucellosis.

Endocarditis occurs in approximately 0.5%–2% of brucellosis patients (see Table 3) and is the most frequent cause of death from brucellosis.[26] Approximately half of endocarditis occurs on unhealthy or prosthetic valves, while the other half occurs on normal valves.[27,28] Most people with brucellar endocarditis require valve replacement surgery and triple antibiotic treatment for 6 weeks to 3 months.[29] After valve replacement and antibiotic therapy, patients are generally cured, with no relapse in symptoms after a prolonged illness of months to a few years.

Neurobrucellosis is another uncommon but severe localized infection of brucellosis and occurs in approximately 1%–7% of brucellosis patients (see Table 3). Most commonly, neurobrucellosis manifests as meningitis, but it can also manifest as stroke or another neurological condition.[30] Headache, weakness, sensory loss, gait disorder, and confusion are common symptoms of neurobrucellosis.[31] When treated promptly with triple antibiotic therapy, neurobrucellosis patients often recover within 3 to 8 months. Some, however, can have prolonged illness or sequelae that last years after the initial treatment.[32] A literature review of 63 patients with neurobrucellosis found that 13 of them had sequelae (20.6%), but the sequelae were not defined.[33] Among seven case reports of neurobrucellosis in

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25 Ziad A. Memish, M. Alazzawi, R. Bannatyne, "Unusual Complication of Breast Implants: *Brucella* Infection," *Infection* 29, no. 5 (October 2001): 291–292, https://link.springer.com/content/pdf/10.1007/s15010-001-1129-3.pdf.

26 J. M. Reguera et al., "*Brucella* Endocarditis: Clinical, Diagnostic, and Therapeutic Approach," *European Journal of Clinical Microbiology & Infectious Diseases* 22, no. 11 (November 2003): 647–650, https://link.springer.com/content/pdf/10.1007%2Fs10096-003-1026-z.pdf.

27 Ibid.

28 Colmenero et al., "Complications Associated with *Brucella melitensis* Infection."

29 Saad S. Al-Harthi, "The Morbidity and Mortality Pattern of *Brucella* Endocarditis," *International Journal of Cardiology* 25, no. 3 (December 1989): 321–324, https://doi.org/10.1016/0167-5273(89)90222-2.

30 Donald R. McLean, Neville Russell, and M. Yousuf Khan, "Neurobrucellosis: Clinical and Therapeutic Features," *Clinical Infectious Diseases* 15, no. 4 (1 October 1992): 582–590, https://doi.org/10.1093/clind/15.4.582.

31 Meltem Arzu Yetkin et al., "Evaluation of the Clinical Presentations of Neurobrucellosis," *International Journal of Infectious Diseases* 10, no. 6 (November 2006): 446–452, https://doi.org/10.1016/j.ijid.2006.05.007.

32 McLean, Russell, and Khan, "Neurobrucellosis: Clinical and Therapeutic Features."

33 Georgios Pappas, Nikolas Akritidis, and Leonidas Christou, "Treatment of Neurobrucellosis: What Is Known and What Remains to Be Answered," *Expert Review of Anti-infective Therapy* 5, no. 6 (December 2007): 983–990, https://doi.org/10.1586/14787210.5.6.983.

Spain, four recovered with no sequelae, two recovered with sequelae, and one died.[34] The two with residual sequelae were a 67-year-old woman with residual partial paralysis of the lower limbs who could still walk with crutches and a 46-year-old man who slowly over many years recovered strength in his legs. Of 20 neurobrucellosis patients in Turkey, 18 fully recovered while two (a 38-year-old female and a 48-year-old male) had residual gait disorders.[35] Of 18 case reports of neurobrucellosis in Saudi Arabia, 12 fully recovered, 1 died, 1 was elderly and in a vegetative state, and 4 had other residual sequelae (22.2%).[36] The four with residual sequelae (not including the one in a vegetative state) had hearing loss, and one had loss of vision in one eye along with hearing loss. They were aged 33, 65, 69, and 70. Therefore, although residual symptoms may be more common among older individuals, they can also occur among young men and women. Residual symptoms of neurobrucellosis include hearing loss and gait disorders.

Early definitions of chronic brucellosis among treated patients described chronic fatigue and psychiatric complaints. The most common symptoms listed were fatigue, headache, insomnia, depression, anxiety, irritability, muscle pain, and sexual impotence.[37] Although this form of chronic brucellosis was commonly described in publications in the 1940s and 1950s, it is generally not mentioned in later publications. Depression, anxiety, and insomnia, symptoms associated with early definitions of "chronic brucellosis," are more common among those who present with brucellosis more than a year after the onset of symptoms, although the incidence is still rare.[38] Thus, although chronic fatigue may still occur with brucellosis, it may also have been associated with the inferior antibiotics used in the 1940s and 1950s. Serology of those with this mild chronic brucellosis, however, is often negative and similar to those who have recovered.[39] Of 17 laboratory workers treated for brucellosis in 1945, 5 had persistent fatigue (29.4%) for at least 5 to 12 months after the initial symptoms of disease had subsided.[40] By 1½ to 2 years after illness, most workers were fully recovered, aside from two with mild occasional symptoms that did not significantly affect their day-to-day lives. Since this chronic fatigue has not been presented in modern treated cases of brucellosis, it is unlikely to occur among the relevant population when treated properly.

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34 Emilio Bouza et al., "Brucellar Meningitis," *Reviews of Infectious Diseases* 9, no. 4 (July–August 1987): 810–822, https://doi.org/10.1093/clinids/9.4.810.

35 Yetkin et al., "Evaluation of the Clinical Presentations of Neurobrucellosis."

36 McLean, Russell, and Khan, "Neurobrucellosis: Clinical and Therapeutic Features."

37 Cluff, Trever, and Imboden, "Brucellosis II."

38 Lulu et al., "Human Brucellosis in Kuwait."

39 Cluff, Trever, and Imboden, "Brucellosis II."

40 Calderon Howe et al., "Acute Brucellosis among Laboratory Workers," *The New England Journal of Medicine* 236, no. 20 (May 15, 1947): 741–747, doi:10.1056/NEJM194705152362003.

Relapse is frequent with brucellosis, even after complying fully with the antibiotic regimen. Ariza et al. found that common risk factors for relapse among 394 Spanish patients included using less effective antibiotics and starting treatment less than 10 days after the onset of symptoms.[41] The most common antibiotics used in the past for brucellosis were a combination of doxycycline and streptomycin or doxycycline and rifampicin, with doxycycline and rifampicin taken for at least 6 weeks and streptomycin taken for at least 2 weeks.[42] Today, a tetracycline combined with rifampicin is the preferred treatment, and streptomycin is no longer used on humans in the United States due to its side effects. Little information is available about noncompliance with brucellosis therapies, but it often appears to be low in studies due to the hospitalization of many individuals with brucellosis and the fact that streptomycin, one of the most commonly prescribed antibiotics for brucellosis in the past in developing countries, must be administered intramuscularly. Table 4 provides the relapse rates associated with combination treatments of a tetracycline + streptomycin or rifampicin. Most studies used antibiotic regimens that lasted 42 days or longer. Regimens that were shorter had higher rates of relapse. Relapse is higher in those given a tetracycline + rifampicin (~5%–15% for those taking both antibiotics for more than 42 days) than those given a tetracycline + streptomycin (~0%–10% for those taking tetracycline for more than 42 days). The tetracycline + rifampicin treatment, however, is easier to administer since both antibiotics can be taken orally, and, as mentioned, streptomycin is no longer used in the United States. Symptoms during relapse mirror the symptoms of acute brucellosis, although they are often milder.[43]

Brucellosis can produce a prolonged infection in untreated individuals, lasting up to 2–3 years. Localized infection can prolong illness in untreated and treated individuals and can lead to death or long-term sequelae if the infection is localized in the heart (endocarditis) or nervous system (neurobrucellosis). In addition, relapse is still common among treated individuals. In many studies, brucellosis patients are followed for 2 years or more after illness to monitor potential sequelae or relapses, and these conditions rarely occur more than 2 years after the initial illness has subsided.

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41 Javier Ariza et al., "Characteristics of and Risk Factors for Relapse in Brucellosis in Humans," *Clinical Infectious Diseases* 20, no. 5 (May 1995): 1241–1249, https://doi.org/10.1093/clinids/20.5.1241.

42 Javier Ariza et al., "Perspectives for the Treatment of Brucellosis in the 21st Century: The Ioannina Recommendations," *PLoS Medicine* 4, no. 12 (2007): e317, doi:10.1371/journal.pmed.0040317.

43 Panos Andriopoulos et al., "Acute Brucellosis: Presentation, Diagnosis, and Treatment of 144 Cases," *International Journal of Infectious Diseases* 11, no. 1 (January 2007): 52–57, https://doi.org/10.1016/j.ijid.2005.10.011.

Table 4. Relapse Rate for Treated Brucellosis

Total # Patients	# Relapsed (Rate)	Location	Antibiotic Regimen	Antibiotic Duration (Days)[a]	Source
64	14 (21.9%)	Spain	rifampicin + doxycycline	28	Montejo (1993)[44]
18	7 (38.8%)	Spain	rifampicin + doxycycline	30	Ariza (1985)[45]
30	1 (3.3%)	Turkey	rifampicin + doxycycline	42	Akova (1993)[46]
45	5 (11.1%)	Spain	rifampicin + doxycycline	42	Montejo (1993)
10	2 (20.0%)	Spain	rifampicin + doxycycline	42	Colmenero (1994)[47]
45	6 (14.3%)	Turkey	rifampicin + doxycycline	42	Ersoy (2005)[48]
173	8 (4.6%)	Turkey	rifampicin + doxycycline	42–84	Aygen (2002)[49]
45	3 (6.7%)	Spain	rifampicin + doxycycline	45	Ariza (1995)[50]
100	16 (16.0%)	Spain	rifampicin + doxycycline	45	Solera (1995)[51]
20	2 (10%)	Turkey	rifampicin + doxycycline	45	Agalar (1999)[52]
30	2 (6.7%)	Turkey	rifampicin + doxycycline	45	Saltoglu (2002)[53]

[44] J. M. Montejo et al., "Open, Randomized Therapeutic Trial of Six Antimicrobial Regimens in the Treatment of Human Brucellosis," *Clinical Infectious Diseases* 16, no. 5 (May 1993): 671–676, https://www.jstor.org/stable/4457047.

[45] J. Ariza et al., "Comparative Trial of Rifampin-Doxycycline Versus Tetracycline-Streptomycin in the Therapy of Human Brucellosis," *Antimicrobial Agents and Chemotherapy* 28, no. 4 (October 1985): 548–551, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC180303/.

[46] Murat Akova et al., "Quinolones in Treatment of Human Brucellosis: Comparative Trial of Ofloxacin-Rifampin Versus Doxycycline-Rifampin," *Antimicrobial Agents and Chemotherapy* 37, no. 9 (September 1993): 1831–1834, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC188077/.

[47] J. D. Colmenero et al., "Possible Implications of Doxycycline-Rifampin Interaction for Treatment of Brucellosis," *Antimicrobial Agents and Chemotherapy* 38, no. 12 (December 1994): 2798–2802, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC188288/.

[48] Yasemin Ersoy et al., "Comparison of Three Different Combination Therapies in the Treatment of Human Brucellosis," *Tropical Doctor* 35, no. 4 (October 2005): 210–212, https://journals.sagepub.com/doi/pdf/10.1258/004947505774938765.

[49] Aygen et al., "Clinical Manifestations, Complications and Treatment of Brucellosis."

[50] Ariza et al., "Characteristics of and Risk Factors for Relapse."

[51] Javier Solera et al., "Doxycycline-Rifampin Versus Doxycycline-Streptomycin in Treatment of Human Brucellosis Due to *Brucella melitensis*," *Antimicrobial Agents and Chemotherapy* 39, no. 9 (September 1995): 2061–2067, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC162881/.

[52] C. Agalar, S. Usubutun, and R. Turkyilmaz, "Ciprofloxacin and Rifampicin Versus Doxycycline and Rifampicin in the Treatment of Brucellosis," *European Journal of Clinical Microbiology and Infectious Diseases* 18, no. 8 (August 1999): 535–538, https://link.springer.com/content/pdf/10.1007/s100960050344.pdf.

[53] Nese Saltoglu et al., "Efficacy of Rifampicin plus Doxycycline Versus Rifampicin Plus Quinolone in the Treatment of Brucellosis," *Saudi Medical Journal* 23, no. 8 (August 2002): 921–924, https://www.ncbi.nlm.nih.gov/pubmed/12235463.

Total # Patients	# Relapsed (Rate)	Location	Antibiotic Regimen	Antibiotic Duration (Days)[a]	Source
25	5 (25%)	Iran	rifampicin + doxycycline	56	Alavi (2009)[54]
24	0 (0%)	Jordan	rifampicin + tetracycline	42	Shehabi (1990)[55]
4	0 (0%)	Turkey	rifampicin + tetracycline	21–42	Aygen (2002)
146	5 (3.4%)	Turkey	streptomycin + doxycycline	21–56	Aygen (2002)
10	1 (10.0%)	Kuwait	streptomycin + doxycycline	42	Lulu (1998)[56]
102	4 (3.9%)	Spain	streptomycin + doxycycline	42	Cisneros (1990)[57]
44	1 (2.3%)	Spain	streptomycin + doxycycline	42	Montejo (1993)
40	3 (7.5%)	Spain	streptomycin + doxycycline	42	Montejo (1993)
10	0 (0%)	Spain	streptomycin + doxycycline	42	Colmenero (1994)
32	3 (9.7%)	Turkey	streptomycin + doxycycline	42	Ersoy (2005)
94	5 (5.3%)	Spain	streptomycin + doxycycline	45	Solera (1995)
125	4 (2.8%)	Greece	streptomycin + doxycycline	60	Andriopoulos (2007)[58]
28	2 (7.1%)	Spain	streptomycin + tetracycline/ doxycycline	30	Ariza (1985)
26	0 (0%)	Israel	streptomycin + tetracycline	21	Samra (1983)[59]
92	7 (7.6%)	Turkey	streptomycin + tetracycline	21–56	Aygen (2002)
218	22 (10.1%)	Spain	streptomycin + tetracycline	30–45	Ariza (1995)
56	1 (1.8%)	Jordan	streptomycin + tetracycline	42	Shehabi (1990)
74	0 (0%)	Kuwait	streptomycin + oxytetracycline	42	Lulu (1998)

[a] Antibiotic duration is given for the antibiotic with the longest course. For example, a treatment regimen with concurrent 14 days of streptomycin and 42 days of tetracycline is listed as 42 days.

54 Syed Muhammad Alavi, Syed Mohammad Reza Alavi, and Leil Alavi, "Relapsed Human Brucellosis and Related Risk Factors," *Pakistan Journal of Medical Science* 25, no. 1 (January–March 2009): 46–50, https://pjms.com.pk/issues/janmar09/article/article8.html.

55 Asem Shehabi et al., "Diagnosis and Treatment of 106 Cases of Human Brucellosis," *Journal of Infection* 20, no. 1 (January 1990): 5–10, https://doi.org/10.1016/S0163-4453(90)92214-6.

56 Lulu et al., "Human Brucellosis in Kuwait."

57 J. M. Cisneros et al., "Multicenter Prospective Study of Treatment of *Brucella melitensis* Brucellosis with Doxycycline for 6 Weeks Plus Streptomycin for 2 Weeks," *Antimicrobial Agents and Chemotherapy* 34, no. 5 (May 1990): 881–883, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC171710/.

58 Andriopoulos et al., "Acute Brucellosis."

59 Y. Samra et al., "Brucellosis: Difficulties in Diagnosis and a Report on 38 Cases," *Infection* 11, no. 6 (November–December 1983): 310–312, https://link.springer.com/content/pdf/10.1007/BF01641353.pdf.

Conclusion: Brucellosis can last up to 2–3 years if left untreated, either presenting as a mild-to-severe illness with no remission or as a relapsing illness with remissions. In treated and untreated individuals, localized infections can produce symptoms for even longer and often require many months of antibiotic treatment and sometimes surgery. Endocarditis (0.5%–2% of patients) and neurobrucellosis (1%–7% of patients) are the most severe localized infections but are rare. Endocarditis generally does not produce sequelae after surgery and antibiotic therapy, although full recovery may take 2–3 years. Those with neurobrucellosis often recover fully after antibiotic therapy, but ~20% of individuals may have sequelae such as gait disorders or hearing loss. Relapse is common among individuals, even those who have complied fully with antibiotic treatment. The standard treatment for brucellosis is a tetracycline + rifampicin, which has a relapse rate of ~5%–15% when given for 42 days or more. Tetracycline + streptomycin has been used in the past and has a relapse rate of ~0%–10% when given for 14 days (streptomycin) and 42 days (tetracycline) or more.

Caveats:

- **Few descriptions of untreated brucellosis are available, and the case reports available appear to describe shorter illness than is often portrayed in larger reports or individuals who report for treatment more than a year after initial symptoms developed.**
- **Many descriptions of neurobrucellosis indicated that people had sequelae without defining what sequelae they had.**

B. Melioidosis

Melioidosis is caused by the bacterium *Burkholderia pseudomallei*.[60] Since the causative agent of melioidosis is closely related to that of glanders, they have similar injury profiles. Like glanders, untreated melioidosis can go into remission and subsequently relapse.[61] Abscesses and fever are common in untreated chronic melioidosis, and years of remission can transpire between relapses.

Treated melioidosis is associated with relatively high rates of relapse. Melioidosis is more common in those who suffer from diabetes, alcoholism, or chronic renal disease. The *AMedP-7.5* model does not include people with these risk factors in the analysis.[62] Unfortunately, most studies on relapse from melioidosis do not separate out those who have risk factors from those who do not, especially not when determining the relapse rate. Therefore,

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60 Nicholas J. Vietri and David Deshazer, "Melioidosis," chap. 7 in *Medical Aspects of Biological Warfare*, ed. Zygmunt F. Dembek, Textbooks of Military Medicine (Washington, DC: Department of Defense, Office of the Surgeon General, U.S. Army, Borden Institute, 2007), https://ke.army.mil/bordeninstitute/published_volumes/biological_warfare/BW-ch07.pdf.

61 Amos L. Prevatt and John S. Hunt, "Chronic Systemic Melioidosis: Review of Literature and Report of a Case, with a Note on Visual Disturbance Due to Chloramphenicol," *American Journal of Medicine* 23, no. 5 (November 1957): 810–823, https://doi.org/10.1016/0002-9343(57)90382-0.

62 Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 22-3.

individuals with those risk factors were still included in this analysis, which may bias the results some since individuals with risk factors tend to have more serious illness.[63]

The treatment regimen for melioidosis is frequently extensive and can last months. An intravenous (IV) antibiotic is first given for approximately 2 weeks, and then an oral antibiotic or combination of antibiotics is given for up to 12 weeks. Two hospitals in Darwin, Australia, and Ubon Ratchatani, Thailand, have tested different antibiotics or characterized the rate of relapse at a given hospital over decades, and other hospitals have tested antibiotic regimens over shorter durations. Table 5 provides a list of studies and the relapse rates reported. Many of the patients who have a relapse of melioidosis, however, do not complete the full oral antibiotic regimen, since it lasts 12 weeks or longer and can cause adverse side effects. In addition, some risk factors for melioidosis, such as alcoholism, can be associated with low drug compliance.[64] Table 5 also provides the number of patients who relapsed even after complying fully with antibiotic treatment. In this analysis, we assume that all military personnel who receive treatment for melioidosis would complete the full regimen. When the full course of antibiotics is taken, the relapse rate is low (<5%).

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[63] Bart J. Currie, Linda Ward, and Allen C. Cheng, "The Epidemiology and Clinical Spectrum of Melioidosis: 540 Cases from the 20 Year Darwin Prospective Study," *PLoS Neglected Tropical Diseases* 4, no. 11 (November 30, 2010): e900, https://doi.org/10.1371/journal.pntd.0000900.

[64] Roger W. Guard et al., "Melioidosis in Far North Queensland: A Clinical and Epidemiological Review of Twenty Cases," *The American Journal of Tropical Medicine and Hygiene* 33, no. 3 (May 1984): 467–473, https://doi.org/10.4269/ajtmh.1984.33.467.

Table 5. Relapse Rate for Treated Melioidosis

Total # Survivors	# Relapsed (Rate)	# Compliant Patients who Relapse	Location	Antibiotic Regimen	Notes	Source
14	3 (21.4%)	0	Queensland, Australia	Not specified	All who relapsed were alcoholics	Guard (1984)[65]
18	0 (0%)	0	Khon Kaen, Thailand	10–14 days: chloramphenicol, doxycycline, trimethoprim + sulfamethoxazole (TMP-SMX); 3–6 months: doxycycline and co-trimoxazole		Sookpranee (1992)[66]
22	0 (0%)	0	Khon Kaen, Thailand	10–14 days: ceftazidime, co-trimoxazole; 3–6 months: doxycycline and co-trimoxazole		Sookpranee (1992)
118	27 (22.9%)	Unknown	Khon Kaen, Thailand	>7 days: ceftazidime, coamoxiclav, or chloram-phenicol, doxycycline, and cotrimoxazole combo; oral: coamoxiclav or chloram-phenicol, doxycycline, and TMP-SMX		Chaowagul (1993)[67]

65 Guard et al., "Melioidosis in Far North Queensland."

66 Mondej Sookpranee et al. "Multicenter Prospective Randomized Trial Comparing Ceftazidime Plus Co-Trimoxazole with Chloramphenicol Plus Doxycycline and Co-Trimoxazole for Treatment of Severe Melioidosis," *Antimicrobial Agents and Chemotherapy* 36, no. 1 (January 1992): 158–162, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC189245/.

67 W. Chaowagul et al., "Relapse in Melioidosis: Incidence and Risk Factors." *The Journal of Infectious Diseases* 168, no. 5 (November 1993): 1181–1185, https://doi.org/10.1093/infdis/168.5.1181.

Total # Survivors	# Relapsed (Rate)	# Compliant Patients who Relapse	Location	Antibiotic Regimen	Notes	Source
52	2 (3.8%)	2 (4.9%)	Ubon Ratchatani, Thailand	Standard IV treatment; 20 weeks: chloramphenicol, cotrimoxazole, and doxycycline	Compliant defined as >12 weeks oral antibiotic	Rajchanuyong (1995)[68]
49	8 (16.3%)	4 (10%)	Ubon Ratchatani, Thailand	Standard IV treatment; 20 weeks: co-amoxiclav	Compliant defined as >12 weeks oral antibiotic	Rajchanuyong (1995)
44	1 (2.3%)	0	Ubon Ratchatani, Thailand	IV treatment: ceftazidime, imipenem, co-amoxiclav; 12 weeks: chloramphenicol, TMP-SMX, doxycycline	Only relapse was from stopping antibiotic at 4 days	Chaowagul (1999)[69]
43	11 (25.6%)	8	Ubon Ratchatani, Thailand	IV treatment: ceftazidime, imipenem, co-amoxiclav; 12 weeks: doxycycline	Inferior treatment	Chaowagul (1999)
207	27 (13.0%)	16	Darwin, Australia	None specified	Subset of Currie (2010)[70]	Currie (2000)[71]

[68] A. Rajchanuyong et al., "A Prospective Comparison of Co-Amoxiclav and the Combination of Chloramphenicol, Doxycycline, and Co-Trimoxazole for the Oral Maintenance Treatment of Melioidosis," *Transactions of the Royal Society of Tropical Medicine and Hygiene* 89, no. 5 (September–October 1995): 546–549, https://www.ncbi.nlm.nih.gov/pubmed/8560537.

[69] Wipada Chaowagul et al., "A Comparison of Chloramphenicol, Trimethoprim-Sulfamethoxazole, and Doxycycline with Doxycycline Alone as Maintenance Therapy for Melioidosis," *Clinical Infectious Diseases* 29, no. 2 (August 1999): 375–380, https://doi.org/10.1086/520218.

[70] Currie, Ward, and Chang, "The Epidemiology and Clinical Spectrum of Melioidosis."

[71] Bart J. Currie et al. "Melioidosis: Acute and Chronic Disease, Relapse and Re-Activation," *Transactions of the Royal Society of Tropical Medicine and Hygiene* 94, no. 3 (May 2000): 301–304, https://doi.org/10.1016/S0035-9203(00)90333-X.

Total # Survivors	# Relapsed (Rate)	# Compliant Patients who Relapse	Location	Antibiotic Regimen	Notes	Source
68	8 (11.8%)	Unknown	Ubon Ratchatani, Thailand	Standard IV treatment; 12 weeks: TMP-SMX, doxycycline, chloramphenicol (until adverse effect)	Poor drug tolerance	Chaowagul (2005)[72]
56	3 (5.4%)	Unknown	Ubon Ratchatani, Thailand	Standard IV treatment; 12 weeks: TMP-SMX, doxycycline (until adverse effect)	Poor drug tolerance	Chaowagul (2005)
889	86 (9.7%)	36 (5.2%)	Ubon Ratcchatani, Thailand	Standard treatment, compli-ance was assumed for those taking >8 weeks oral antibiotics	1986–2004, so includes some from Chaowagul studies	Limmathurotsakul (2006)[73]
30	4 (13.3%)	Unknown	Tainan City, Taiwan	None specified	Retrospective study	Chou (2007)[74]

[72] Wipada Chaowagul et al., "Open-Label Randomized Trial of Oral Trimethoprim-Sulfamethoxazole, Doxycycline, and Chloramphenicol Compared with Trimethoprim-Sulfamethoxazole and Doxycycline for Maintenance Therapy of Melioidosis," *Antimicrobial Agents and Chemotherapy* 49, no. 10 (2005): 4020–4025, doi:10.1128/AAC.49.10.4020-4025.2005.

[73] Direk Limmathurotsakul et al., "Risk Factors for Recurrent Melioidosis in Northeast Thailand," *Clinical Infectious Diseases* 43, no. 8 (15 October 2006): 979–986, https://doi.org/10.1086/507632.

[74] Deng-Wei Chou et al., "Bacteremic Melioidosis in Southern Taiwan: Clinical Characteristics and Outcome," *Journal of the Formosan Medical Association* 106, no. 12 (December 2007): 1013–1022, https://doi.org/10.1016/S0929-6646(08)60077-7.

Total # Survivors	# Relapsed (Rate)	# Compliant Patients who Relapse	Location	Antibiotic Regimen	Notes	Source
465	25 (5.4%)	Unknown	Darwin, Australia	Standard treatment	1989–2009, relapse was associated with poor drug compliance, but no numbers given	Currie (2010)[75]
311	16 (5.1%)	Unknown	5 hospitals, northeast Thailand	Standard IV treatment, 12–20 weeks: TMP-SMX and placebo	82% received oral treatment for >8 weeks	Chetchotisakd (2014)[76]
315	21 (7.0%)	Unknown	5 hospitals, northeast Thailand	Standard IV treatment, 12–20 weeks: TMP-SMX and doxycycline	82% received oral treatment for >8 weeks	Chetchotisakd (2014)
218	1 (0.4%)	0	Darwin, Australia	Standard treatment	Oct. 2009–Sep. 2012, one relapse. Took no oral antibiotic	Pitman (2015)[77]

[75] Currie, Ward, and Cheng, "The Epidemiology and Clinical Spectrum of Melioidosis."

[76] Ploenchan Chetchotisakd et al., "Trimethoprim-Sulfamethoxazole versus Trimethoprim-Sulfamethoxazole Plus Doxycycline as Oral Eradicative Treatment for Melioidosis (MERTH): A Multicentre, Double-Blind, Non-Inferiority, Randomised Controlled Trial," *The Lancet* 383, no. 9919 (March 01, 2014): 807–814, https://doi.org/10.1016/S0140-6736(13)61951-0.

[77] Matthew C. Pitman et al., "Intravenous Therapy Duration and Outcomes in Melioidosis: A New Treatment Paradigm," *PLoS Neglected Tropical Diseases* 9, no. 3 (March 2015): e0003586, doi:10.1371/journal.pntd.0003586.

Conclusion: Untreated melioidosis has symptoms and pathology similar to untreated glanders, with remission between acute illnesses and relapse characterized by fever and abscesses. Treated melioidosis has a relatively high rate of relapse, although many of the cases of relapse are associated with poor treatment compliance. Among those who complete the full oral antibiotic regimen (>12 weeks), relapse is infrequent (<5% of cases).

Caveats:

- **Few descriptions of untreated melioidosis are available, so the rate of recurrence could not be determined.**
- **Most people who contract melioidosis have risk factors (e.g., diabetes or alcoholism) that would not occur in a military population. These people might have more severe illness and higher rates of relapse than those with no risk factors, but little data are available to enable a comparison.**
- **Although many studies gave the number of individuals who relapsed and did not comply with the antibiotic regimen, these studies did not give the number of individuals who did not relapse and did not comply with the antibiotic regimen, so a relapse rate for compliant individuals could not be calculated.**

C. Q Fever

Q fever is caused by the bacterium *Coxiella burnetii* and generally produces flu-like symptoms that resolve within 1 to 3 weeks.[78] In rare cases, however, serious long-term complications can develop from treated and untreated Q fever. The most commonly referenced chronic effect of Q fever is endocarditis, which can occur up to 10 years after the initial illness.[79] The rate of endocarditis is approximately 0.5%–2%, although in some reports the percent is higher (see Table 6). In addition, since Q fever is a flu-like febrile illness, many individuals never report to a hospital with their symptoms, so long-term effects may be overreported compared to those who recovered fully and never went to a hospital. Almost all people who develop Q fever endocarditis have previous valve defects or diseases. In all but one study, the rate of previous valve defects among Q fever endocarditis patients was 90%–100% (see Table 6). In a military population, the number of people with previous valve defects is anticipated to be very low; however, if exposed individuals do have a history of valve defects, they should be closely monitored. Endocarditis can require years of antibiotic treatment and surgery to be fully resolved and can have a high mortality rate depending on the treatment and time to diagnosis.[80] It is recommended that endocarditis patients be monitored for at least 5 years after treatment ends to ensure that relapse does not occur and that recovery is complete.

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78 Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 24-1, 24-9.

79 S. R. Palmer and S. E. J. Young, "Q-Fever Endocarditis in England and Wales. 1975–81," *The Lancet* 320, no. 8313 (December 25, 1982): 1448–1449, https://doi.org/10.1016/S0140-6736(82)91341-1.

80 Matthieu Million et al., "Long-Term Outcome of Q Fever Endocarditis: A 26-Year Personal Survey," *Lancet Infectious Diseases* 10, no. 8 (August 2010): 527–535, https://doi.org/10.1016/S1473-3099(10)70135-3.

Table 6. Rate of Q Fever Endocarditis

# Patients	# Endocarditis (Rate)	# Endocarditis with Previous Valvulopathy	Location	Source
Unknown	13	12 (92.3%)	Australia	Wilson (1976)[81]
839	92 (11%)	30 (33%)	United Kingdom	Palmer (1982)[82]
111	1 (0.9%)	Unknown	Australia	Spelman (1982)[83]
Unknown	10	9 (90%)	Ireland	Tobin (1982)[84]
249	14 (5.6%)	13 (92.9%)	Spain	Tellez (1988)[85]
Unknown[a]	102	95 (93%)	France	Fenollar (2001)[86]
1569	12 (0.7%)	12 (100%)	France	Fenollar (2001)

[a] The 102 endocarditis patients represent a retrospective look at medical reports of Q fever endocarditis. The 1,569 patients are patients who initially presented to the reference center as acute cases and later developed endocarditis.

Q fever can also localize in other areas of the body, but this condition is generally much rarer than endocarditis. Vascular infection was commonly observed during an outbreak of Q fever in the Netherlands between 2007 and 2010—even more than endocarditis.[87] Vascular infection has also been observed in other outbreaks, although not as frequently.[88] The treatment concerns for vascular infection also apply for endocarditis, and, like endocarditis, vascular infection is much more common in those with previous cardiovascular disease or disorders. Some individuals have had osteomyelitis from Q fever, which resolves with a further regimen of antibiotics.[89] Chronic hepatitis has also been

[81] H. G. Wilson et al., "Q Fever Endocarditis in Queensland," *Circulation* 53, no. 4 (April 1976): 680–684, https://www.ahajournals.org/doi/pdf/10.1161/01.CIR.53.4.680.

[82] Palmer and Young, "Q-Fever Endocarditis in England and Wales."

[83] Denis W. Spelman, "Q Fever: A Study of 111 Consecutive Cases," *Medical Journal of Australia* 1, no. 13 (June 26, 1982): 547–553, https://www.cabdirect.org/cabdirect/abstract/19832703765.

[84] M. J. Tobin et al., "Q Fever Endocarditis," *The American Journal of Medicine* 72, no. 3 (March 1982): 396–400, http://dx.doi.org/10.1016/0002-9343(82)90495-8.

[85] A. Tellez et al., "Q Fever in Spain: Acute and Chronic Cases, 1981–1985," *Reviews of Infectious Diseases* 10, no. 1 (January-February 1988): 198–202, https://www.ncbi.nlm.nih.gov/pubmed/3353629.

[86] Florence Fenollar et al., "Risks Factors and Prevention of Q Fever Endocarditis," *Clinical Infectious Diseases* 33, no. 3 (August 2001): 312–316, https://doi.org/10.1086/321889.

[87] Linda M. Kampschreur et al., "Chronic Q Fever in the Netherlands 5 Years after the Start of the Q Fever Epidemic: Results from the Dutch Chronic Q Fever Database," *Journal of Clinical Microbiology* 52, no. 5 (April 2014): 1637–1643, doi:10.1128/JCM.03221-13.

[88] Didier Raoult et al., "Q Fever 1985–1998: Clinical and Epidemiologic Features of 1,383 Infections," *Medicine* 79, no. 2 (March 2000): 109–123, https://www.ncbi.nlm.nih.gov/pubmed/10771709.

[89] Philippe Brouqui et al., "Chronic Q Fever: Ninety-Two Cases from France, Including 27 Cases without Endocarditis," *Archives of Internal Medicine* 153, no. 5 (1993): 642–648, doi:10.1001/archinte.1993.00410050074010.

described and was cleared with antibiotics.[90] Infection of the eye with Q fever has been documented in nine case reports.[91] Of these nine individuals, six had sequelae that lasted longer than 3 months. The sequelae observed were generally blurry vision, vision loss (partial or full), and/or pupil defects.[92] Most individuals were not followed up with for more than a year after the acute illness, although little or no improvement had occurred in eyesight at that time.

Meningitis and other neurological conditions (aside from headache) have been observed rarely in association with acute Q fever.[93] In a study of 121 acute Q fever patients in Greece, 5 patients (4.1%) had confusion and 1 patient (0.8%) had meningitis.[94] Neurological sequelae can sometimes occur following these acute symptoms. In Plymouth, United Kingdom, 103 patients total had acute Q fever, 10 of whom had neurological symptoms (9.7%).[95] Of those 10 patients, 3 fully recovered, 3 were not followed up with after the first 2 months, and 4 had sequelae. One had minimal leg weakness and weight loss at 1 year and was an alcoholic. One had recurrent meningitis, tender arms, blurred vision, and periorbital pain for 3 years after illness. One had recurrent headaches, shoulder pain, and numbness in the left leg for 5 years. The last had mental slowness and leg weakness for the first 7 years, which worsened for the next 7 years and resolved partially 14 years after the acute illness.[96] Among 1,269 patients who had acute Q fever in France, 29 (2.3%) had neurological symptoms, 22 (1.7%) had complete recovery within weeks, and 7 (0.6%) had neurological sequelae, likely permanent in four of the cases.[97] The nature of those sequelae was not given.

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90 Patrick Atienza et al., "Chronic Q Fever Hepatitis Complicated by Extensive Fibrosis," *Gastroenterology* 95, no. 12 (August 1988): 478–481, https://doi.org/10.1016/0016-5085(88)90507-0.

91 Chong Ong et al., "Optic Neuritis Associated with Q Fever: Case Report and Literature Review," *International Journal of Infectious Diseases* 14, Supplement 3 (September 2010): e269–e273, https://doi.org/10.1016/j.ijid.2009.11.010.

92 Ibid.

93 S. Reilly, J. L. Northwood, and E. O. Caul, "Q Fever in Plymouth, 1972–88: A Review with Particular Reference to Neurological Manifestations," *Epidemiology and Infection* 105, no. 2 (October 1990): 391–408, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2271878/.

94 Diamantis P. Kofteridis et al., "Neurological Complications of Acute Q Fever Infection," *European Journal of Epidemiology* 19, no. 11 (2004): 1051–1054, https://link.springer.com/article/10.1007/s10654-004-0108-2.

95 Reilly, Northwood, and Caul, "Q Fever in Plymouth, 1972–88."

96 Ibid.

97 Emmanuelle Bernit et al., "Neurological Involvement in Acute Q Fever: A Report of 29 Cases and Review of the Literature," *Archives of Internal Medicine* 162, no. 6 (March 25, 2002): 693–700, https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/211336.

Independent from any neurological manifestations during the acute illness, chronic fatigue following recovery from acute Q fever has been well-documented but is still a matter of controversy. Chronic fatigue syndrome has formal criteria, including persistent or relapsing fatigue for at least 6 months that causes a substantial decrease in activity and is not resolved by rest.[98] Chronic fatigue syndrome is more common in those with a history of Q fever than it is in controls.[99] Other symptoms more common in people who have recovered from Q fever include feelings of tiredness (not associated with the full chronic fatigue syndrome), sweating, breathlessness, and blurred vision.[100] Q fever chronic fatigue syndrome is not related to continued bacterial infection.[101] Most studies of Q fever chronic fatigue syndrome have been done through mailed questionnaires and have come from a 1989 outbreak of Q fever in the United Kingdom and the 2007–2010 outbreak of Q fever in the Netherlands.

The percentage of people reporting chronic fatigue syndrome decreases over time following the acute Q fever infection, but levels off at approximately 20%. Among people who were infected with Q fever during the 1989 UK outbreak, 42.3% reported symptoms consistent with chronic fatigue syndrome (compared to 26% of controls) 5 years after the outbreak.[102] At 10 years after the outbreak, 14 of 72 (19.4%) former Q fever patients had chronic fatigue syndrome but only 3 of 72 (4.2%) controls did. For people who had Q fever during the Dutch outbreak, 245 of 336 (73%) patients reported severe fatigue at 3 months, 202 (60%) patients at 12 months, and 124 (37%) patients at 24 months.[103]

The rate of severe fatigue is often higher in Q fever patients, but the difference does not always translate to chronic fatigue syndrome, since chronic fatigue syndrome has a specific symptom profile beyond just severe fatigue. In following individuals via questionnaire 2 years after an outbreak in Jena, Germany, researchers discovered that the rate of fatigue symptoms was higher in those with a history of Q fever than in the controls (54.8 vs.

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98 William C. Reeves et al., "Chronic Fatigue Syndrome – A Clinically Empirical Approach to Its Definition and Study." *BMC Medicine* 3 (December 2005): 19. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1334212/.

99 J. G. Ayres et al., "Long-Term Follow-up of Patients from the 1989 Q Fever Outbreak: No Evidence of Excess Cardiac Disease in Those with Fatigue," *Quarterly Journal of Medicine* 95, no. 8 (August 2002): 539–546, https://www.ncbi.nlm.nih.gov/pubmed/12145393.

100 J. G. Ayres et al., "Post-Infection Fatigue Syndrome Following Q Fever," *Quarterly Journal of Medicine* 91, no. 2 (February 1998): 105–123, https://www.ncbi.nlm.nih.gov/pubmed/9578893.

101 Stephan P. Keijmel et al., "Effectiveness of Long-term Doxycycline Treatment and Cognitive Behavioral Therapy on Fatigue Severity in Patients with Q Fever Fatigue Syndrome (Qure Study): A Randomized Controlled Trial," *Clinical Infectious Diseases* 64, no. 8 (15 April 2017): 998–1005, https://doi.org/10.1093/cid/cix013.

102 Ayres et al., "Post-Infection Fatigue Syndrome Following Q Fever."

103 Joris A. F. van Loenhout et al., "Q-Fever Patients Suffer from Impaired Health Status Long after the Acute Phase of Illness: Results from a 24-Month Cohort Study," *Journal of Infection* 70, no. 3 (March 2015): 237–246, https://doi.org/10.1016/j.jinf.2014.10.010.

20% for fatigue, 32.1 vs. 4.7% for chronic fatigue) but that the rate of chronic fatigue syndrome was no different between the two groups.[104] Those with chronic fatigue had higher scores for psychosocial complaints and hypochondria scales. Cognitive behavioral therapy has been effective in reducing fatigue severity after Q fever, indicating that there may be psychological components to the problem.[105]

In conclusion, Q fever usually resolves completely with a few weeks; however, very rarely (<1% of cases), serious long-term effects can occur. These long-term symptoms can include endocarditis, vascular infection, or neurological sequelae. Endocarditis and vascular infection occur almost entirely in patients with a previous history of valve disease or disorder. Chronic fatigue is a potential long-term effect of Q fever that occurs in approximately 20% of patients, although the presence of chronic fatigue and whether it is psychosomatic is still hotly contested. Information on long-term effects from the Dutch outbreak is still being published, although debate continues about whether the Dutch have cast too wide a net on what constitutes "chronic Q fever" and may include patients with only antibodies from the disease and no prior acute symptoms.[106] Other scientists recommended including only those with acute symptoms and positive results from a polymerase chain reaction (PCR)-based test.[107] In addition, *Coxiella burnetii* was one of the agents tested during the Project Whitecoat program at Fort Detrick, Maryland, which evaluated the effect of pathogens on human subjects. No long-term studies of the military research volunteers have been found for specific biological agents, although the Army is now providing comprehensive medical care to the individuals following a lawsuit.[108] It is possible that information on long-term effects of Q fever may come from this enhanced care.

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[104] Bernhard Strauss et al., "Are Fatigue Symptoms and Chronic Fatigue Syndrome Following Q Fever Infection Related to Psychosocial Variables?" *Journal of Psychosomatic Research* 72, no. 4 (April 2012): 300–304, https://doi.org/10.1016/j.jpsychores.2012.01.010.

[105] Keijmel et al., "Effectiveness of Long-term Doxycycline Treatment and Cognitive Behavioral Therapy."

[106] Dennis G. Barten et al., "Localizing Chronic Q Fever: A Challenging Query," *BMC Infectious Diseases* 13, no. 1 (September 3, 2013): 413, doi:10.1186/1471-2334-13-413.

[107] Didier Raoult, "Chronic Q Fever: Expert Opinion versus Literature Analysis and Consensus," *Journal of Infection* 65, no. 2 (August 2012): 102–108, https://doi.org/10.1016/j.jinf.2012.04.006.

[108] Kathleen Curthoys, "Army to Give Medical Care to Vets Involved in Chemical, Biological Testing," *Army Times*, November 8, 2017, https://www.armytimes.com/news/your-army/2017/11/08/army-to-give-medical-care-to-vets-involved-in-chemical-biological-testing/.

Conclusion: In most people, Q fever resolves within 1 to 3 weeks, with or without treatment. In a small number of cases (<1%), Q fever can lead to endocarditis or vascular infection. These conditions occur almost entirely in people with a history of valve disorders or disease (>90%). Endocarditis or valve disease is anticipated to be even less frequent in a military population. Other very rare complications of Q fever, including neurological sequelae, eye problems, and hepatitis, have been reported. Chronic fatigue syndrome has been more frequent, stabilizing at approximately 20% of people 2 years after acute Q fever, but debate continues about the nature of this illness and whether it is psychosomatic.

Caveats:

- **Chronic fatigue syndrome is still debated as a chronic effect from Q fever.**
- **Because Q fever is usually a flu-like illness, many individuals recover without ever reporting to a hospital, suggesting that the rates of long-term effects are lower than reported.**
- **Neurological sequelae were not always well-described.**
- **Eye problems, hepatitis, or other rare localizations were only described in case reports, so the rate of incidence could not be determined (but is anticipated to be very low).**
- **The Dutch outbreak data from 2007 to 2010, the largest collection of Q fever data, uses a more expansive diagnosis of chronic Q fever than most other studies, allowing antibiotic titers and non-specific chronic symptoms to be used to diagnose chronic Q fever without requiring a history of acute Q fever symptoms or positive PCR results.**

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3. Long-Term Effects of Chemical Agents

Information on the long-term effects of chemical agents typically comes from accidental or intentional exposures through factory accidents, terrorist attacks, warfare, or other events. Virtually all reported exposures to chemical agents are treated, so little information about long-term effects from untreated exposures was found. Part I of this analysis described the long-term effects of five chemical agents in full, but three agents or agent classes had too much information available in the literature to be able to finish the full analysis with a quick-look review.[109] This paper (Part II) completes the literature review of three agents or agent classes: nerve agents, sulfur mustard (HD), and chlorine (Cl_2). In addition to the concluded long-term effects from each agent or agent class, appropriate caveats to the study and gaps in the literature are also presented.

A. Nerve Agents

Chemical nerve agents are some of the deadliest substances known and have been used previously in the Iran-Iraq War and in terrorist attacks in Tokyo and Matsumoto, Japan. Concerns from nerve agent exposures by U.S. soldiers, civilians in Tokyo and Matsumoto, and other groups have led the U.S. and Japanese governments to commission multiple studies on the long-term effects.[110] Most of these reports have focused on the long-term effects of sarin, but the long-term effects of other nerve agents have also occasionally been studied. Most of the recorded sequelae following nerve agent exposure are mild, although some individuals who are not treated promptly can have brain damage from severe or very severe nerve agent exposure secondary to seizures and consequently suffer more major neurological effects.[111] In this review, each of the five nerve agents described in *AMedP-7.5*—tabun (GA), sarin (GB), soman (GD), cyclosarin (GF), and VX—are discussed for their potential to cause long-term effects.[112] Although the long-term effects of OP insecticides have been extensively studied elsewhere, they are not reviewed here. Many

[109] Bishop and Curling, *Analysis of Non-Acute, Sub-Lethal Chemical/Biological Injuries and Illnesses*.

[110] Institute of Medicine, *Gulf War and Health: Updated Literature Review of Sarin* (Washington, DC: The National Academies Press, 2004), https://doi.org/10.17226/11064.

[111] N. Yanagisawa, H. Morita, and T. Nakajima, "Sarin Experiences in Japan: Acute Toxicity and Long-Term Effects," *Journal of the Neurological Sciences* 249, no. 1 (1 November 2006): 76–85, https://doi.org/10.1016/j.jns.2006.06.007.

[112] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*," 6-1.

properties of OP insecticides, such as sequestration in fat tissue, can lead to more long-term effects than those that would be expected from nerve agents.[113] Therefore, it is not always possible to correlate sequelae from exposure to OP insecticides to sequelae from nerve agent exposure.

1. Sarin (GB)

Sarin has been the most extensively studied nerve agent for long-term effects. Most of this effort comes from the exposure of U.S. soldiers to sarin or from the Tokyo and Matsumoto sarin attacks. The largest review of long-term effects from sarin came from a study commissioned after the destruction of rockets that contained sarin and cyclosarin in Khamisiyah, Iraq.[114] No one had acute symptoms of nerve agent exposure, but some complained of later symptoms known as "Gulf War syndrome," leading to questions of whether the low doses of nerve agents could produce those symptoms. The study looked not only at the long-term effects of low doses of sarin, but also at the long-term effects of higher doses of sarin. The most common effects found were mild: small changes in electroencephalogram (EEG) results, insomnia, or memory performance.[115] Ocular effects, especially pupil acclimation to low light, can take 6–8 weeks to resolve and are generally the last non-neurological symptom to recover.[116] Long-term effects of sarin have been studied in larger scale exposures, such as the Tokyo subway attack, in accidental exposures involving few people, and in animals.

a. Human exposures: U.S. Army program

Between 1917 and 1975, the U.S. Army conducted experiments to test the effects and properties of chemical agents, including sarin, after World War II. Between 1955 and 1975, experiments included tests on military volunteers, generally at doses that only produced mild acute symptoms. The people who were either accidentally or intentionally exposed in these experiments were followed up with at least until the end of the acute illness, although sometimes longer. Almost everyone reported no significant sequelae following his exposures, even those who had severe accidental exposures; however, a few reported some neurological or psychological effects. Grob et al. described four case reports of accidental

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[113] Nancy B. Munro, Kathleen R. Ambrose, and Annetta P. Watson, "Toxicity of the Organophosphate Warfare Agents GA, GB, and VX: Implications for Public Protection," *Environmental Health Perspectives* 102, no. 1 (January 1994): 18–38, doi:10.1289/ehp.9410218.

[114] Institute of Medicine, *Gulf War and Health*.

[115] Ibid, 6.

[116] John H. McDonough, "Performance Impacts of Nerve Agents and Their Pharmacological Countermeasures," *Military Psychology* 14, no. 2 (2002): 93–119, https://doi.org/10.1207/S15327876MP1402_3.

exposures to sarin that ranged from mild to severe.[117] All the people recovered within 10 days. Gaon and Werne reported 328 cases of sarin exposure (almost all mild) at Rocky Mountain Arsenal between 1953 and 1954.[118] Of 182 people followed up with for more than 21 days, 23 had lingering neurological symptoms. All were treated with at least atropine tablets soon after exposure. Some reported becoming more reckless or foolish the first month after exposure, and one man complained a few months after two accidental exposures that he was worse at math and more absentminded.[119] Sidell reported that of four people accidentally exposed to sarin at Edgewood Chemical Biological Center (ECBC), three individuals had only mild acute symptoms and completely recovered within 2 months.[120] One individual had very severe acute symptoms and mostly recovered after 2 weeks. He was rehospitalized 4 months afterwards for easy fatigability, pain, and dyspnea upon exertion caused by heart problems. He also complained of depression and anxiety and died 18 months after the accident from a heart attack. It was not known whether his depression, anxiety, or heart problems were related to his exposure to sarin.[121]

Military volunteers who were intentionally exposed to sarin or other nerve agents were generally given much smaller doses, but there was still some concern that they may exhibit long-term symptoms from their exposures. Because of this concern, questionnaires were sent to military volunteers exposed to sarin or other nerve agents 10–30 years after their exposures. No differences in mortality were found between volunteers exposed to nerve agent and the control volunteers.[122] Those chosen to be controls, however, were often in worse health than those chosen to receive nerve agents, confounding the results. Questionnaires sent 10–15 years after exposure concentrated almost entirely on life-altering effects, such as inability to work or hospitalization, and found no differences between exposed and control volunteers.[123] The questionnaire therefore missed any potential smaller effects (e.g., forgetfulness or insomnia) that have been found in others exposed to

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[117] David Grob, "The Manifestations and Treatment of Poisoning Due to Nerve Gas and Other Organic Phosphate Anticholinesterase Compounds," *AMA Archives of Internal Medicine* 98, no. 2 (August 1956): 221–239, doi:10.1001/archinte.1956.00250260095010.

[118] M. D. Gaon and Jacob Werne, *Report of a Study of Mild Exposures to GB at Rocky Mountain Arsenal*, Technical Report AD-130 96 (Denver, CO: Rocky Mountain Arsenal, 1955).

[119] Ibid, 32–38.

[120] Frederick R. Sidell, "Soman and Sarin: Clinical Manifestations and Treatment of Accidental Poisoning by Organophosphorus," *Clinical Toxicology* 7, no. 1 (1974): 1–17, https://doi.org/10.3109/15563657408987971.

[121] Ibid.

[122] National Research Council, *Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents, Volume 1: Anticholinesterases and Anticholinergics* (Washington, DC: National Academy Press, June 1982), https://www.ncbi.nlm.nih.gov/books/NBK217774/.

[123] National Research Council, *Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents, Volume 3: Final Report: Current Health Status of Test Subjects* (Washington, DC: The National Academies Pres, 1985), 25, https://www.ncbi.nlm.nih.gov/books/NBK222994/.

sarin. When phone surveys of 1,339 military volunteers exposed to nerve agents 25–45 years previously were conducted, only very minor increases in sleep disturbance and decreases in attention problems were found among those exposed to nerve agents compared to the controls.[124] Those who reported exposure to chemical agents outside their experience at ECBC reported higher rates of psychological or neurological effects, but those instances included other chemical agents besides nerve agents and were unsubstantiated. A similar program in the United Kingdom exposed eight military volunteers to sarin vapor and found that after mild exposure, the volunteers had increased "jitter" in the first few days after exposure and in follow-ups 4–15 months after exposure.[125] Their results returned to normal by 30 months after exposure. Jitter is a sign of potential failure of signal transmission between neurons and muscles.

b. Human exposures: Tokyo and Matsumoto

The best-studied group for long-term effects of sarin were those exposed in the 1994 and 1995 terrorist attacks in Matsumoto and Tokyo, Japan, by the group Aum Shinrikyo. Most people were only mildly exposed to sarin, but many had severe or very severe acute symptoms and 20 died: 8 in Matsumoto and 12 in Tokyo. Many people reported lingering psychological or neurological symptoms following the attack, although post-traumatic stress disorder (PTSD) was also common after the attack, affecting approximately 9%–14% of those exposed in Tokyo.[126] Surveys of those exposed in Matsumoto found that those who had acute symptoms of sarin exposure reported much higher levels of fatigue and weakness than those who had not been exposed at 1 and 3 years after exposure.[127] Similar increases in tiredness and fatigue, as well as some reported vision difficulties, were observed among the Tokyo victims.[128] Insomnia was also higher in victims compared to controls.[129] Most of these psychological symptoms were difficult to separate from PTSD.

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[124] William F. Page, "Long-Term Health Effects of Exposure to Sarin and Other Anticholinesterase Chemical Warfare Agents," *Military Medicine* 168, no. 3 (March 2003): 239–245, https://www.ncbi.nlm.nih.gov/pubmed/12685692.

[125] D. J. Baker and E. Michael Sedgwick, "Single Fibre Electromyographic Changes in Man after Organophosphate Exposure," *Human and Experimental Toxicology* 15, no. 5 (May 1996): 369–375, https://doi.org/10.1177/096032719601500501.

[126] Noriko Kawana, Shin-ichi Ishimatsu, Katsuya Kanda, "Psycho-Physiological effects of the Terrorist Sarin Attack on the Tokyo Subway System," supplement, *Military Medicine* 166, no. 12: 23–26, https://www.ncbi.nlm.nih.gov/pubmed/11778423.

[127] Tamie Nakajima et al., "Sequelae of Sarin Toxicity at One and Three Years after Exposure in Matsumoto, Japan," *Journal of Epidemiology* 9, no. 5 (November 1999), 337–343, https://doi.org/10.2188/jea.9.337.

[128] Kawana, Ishimatsu, Kanda, "Psycho-Physiological effects of the Terrorist Sarin Attack."

[129] Tomoyuki Kawada et al., "Insomnia as a Sequela of Sarin Toxicity Several Years after Exposure in Tokyo Subway Trains," *Perceptual and Motor Skills* 100, no. 3, Pt. 2 (June 2005): 1121–1126, https://doi.org/10.2466/pms.100.3c.1121-1126.

More extensive testing on 18 victims found that most lingering symptoms were due to PTSD, except for the digit symbol task, which tests psychomotor performance.[130] A study of 56 first responders from Tokyo 3 years after the attack found a dose-dependent decline in performance unrelated to PTSD on a memory test, but no change in any other neurobehavioral, stabilometry, or vibration measurement tests.[131]

Only a few individuals had significant long-term effects from their exposures. One individual from Tokyo remained in a coma for a significant period after the attack.[132] Another had retrograde amnesia, personality changes, and problems with consolidating new learning 6 months after the attack.[133] Everyone else either died or recovered and experienced only the mild long-term effects described earlier.

c. Human exposures: Other

A few other human exposures to sarin that were not related to either the U.S. program or the Japanese terrorist attacks have been reported. Most of these findings were similar to those found in the first two groups. Duffy et al. studied the EEG results of 77 factory workers who had documented accidental exposure to sarin at least 1 year previously.[134] They found that those who had been exposed to sarin had significantly more rapid eye movement (REM) during sleep than control individuals. REM is associated with dreaming. Both groups had less REM sleep than normal, however, possibly because of the new sleep environment.[135] The change in EEG pattern was also observed 1 year after sarin exposure in rhesus monkeys.[136]

Although tabun and sarin were used as chemical warfare agents during the Iran-Iraq War, little follow-up was done on Iranian soldiers who were exposed. One study of late complications of the skin found that those exposed to nerve agents had significantly more

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[130] K. Yokoyama et al., "Chronic Neurobehavioral Effects of Tokyo Subway Sarin Poisoning in Relation to Posttraumatic Stress Disorder," *Archives of Environmental Health* 53, no. 4 (July–August 1998): 249–256, https://www.ncbi.nlm.nih.gov/pubmed/9709988.

[131] Yuji Nishiwaki et al., "Effects of Sarin on the Nervous System in Rescue Team Staff Members and Police Officers 3 Years after the Tokyo Subway Sarin Attack," *Environmental Health Perspectives* 109, no. 11 (November 2001): 1169–1173, doi:10.1289/ehp.011091169.

[132] Yanagisawa, Morita, and Nakajima, "Sarin Experiences in Japan."

[133] Kotaro Hatta et al., "Amnesia from Sarin Poisoning," *The Lancet* 347, no. 9011 (11 May 1996): 1343, https://doi.org/10.1016/S0140-6736(96)90998-8.

[134] Frank H. Duffy et al., "Long-Term Effects of an Organophosphate upon the Human Electroencephalogram," *Toxicology and Applied Pharmacology* 47, no. 1 (January 1979): 161–176, https://doi.org/10.1016/0041-008X(79)90083-8.

[135] Ibid.

[136] James L. Burchfiel, Frank H. Duffy, and Van M. Sim, "Persistent Effects of Sarin and Dieldrin upon the Primate Electroencephalogram," *Toxicology and Applied Pharmacology* 35, no. 2 (February 1976): 365–379, https://doi.org/10.1016/0041-008X(76)90296-9.

acne and small fungal infections than those exposed to sulfur mustard.[137] These skin symptoms were likely related to stress since those exposed to nerve agents had higher rates of PTSD than those exposed to sulfur mustard.[138] In Iraq in 2004, two U.S. Army officers were exposed to sarin while picking up an improvised explosive device (IED).[139] Both had moderate acute symptoms. One fully recovered, and the other complained for the next 8 months about short-term memory loss, dyscoordination, and episodic imbalance, although none of the symptoms were severe enough to affect his work performance. He was sent for neuropsychological testing 8 months after exposure, and he had difficulties with the short-term memory and tasks that required attention.[140] The study did not report whether the soldier recovered after that.

d. Animal studies

In addition to reports of human exposure, long-term effects of sarin have been studied in animals. Many animal studies of nerve agents use injection rather than aerosol to expose the animals. For this analysis, the short- and long-term effects observed in these animals appear to be similar to the effects by injection and inhalation. Therefore, results from both exposure types are summarized here.

Animal studies provide additional insight into long-term effects on untreated animals and long-term effects from doses that could be lethal. One effect that has been observed following OP insecticide exposure is delayed neuropathy, which is a paralysis of the limbs 8–14 days after exposure.[141] Although it can be common after exposure to some insecticides, it generally only occurs in pretreated animals given very large doses of nerve agents. Hens pretreated with atropine, physostigmine, and oximes and then given a dose of 30–60 times the dose of sarin that produces lethal effects in 50% of the population (LD_{50}) developed delayed neuropathy.[142] These conditions are unlikely in a real-world setting, however, so delayed neuropathy is not anticipated to occur.

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[137] Seyed Naser Emadi, Mohammadreza Mortazavi, and Hossein Mortazavi, "Late Cutaneous Manifestations 14 to 20 Years after Wartime Exposure to Sulfur Mustard Gas: A Long-Term Investigation," *Archives of Dermatology* 144, no. 8 (August 2008): 1059–1061, doi:10.1001/archderm.144.8.1059.

[138] Ibid.

[139] Yince Loh et al., "Case Report: Long-Term Cognitive Sequelae of Sarin Exposure," *NeuroToxicology* 31, no. 2 (March 2010): 244–246, https://doi.org/10.1016/j.neuro.2009.12.004.

[140] Ibid.

[141] Munro et al., "Toxicity of the Organophosphate Warfare Agents."

[142] James J. Gordon et al., "The Delayed Neuropathic Effects of Nerve Agents and Some Other Organophosphorus Compounds," *Archives of Toxicology* 52, no. 2 (February 1983): 71–82, https://link.springer.com/article/10.1007/BF00354767.

High levels of sarin exposure in rats, mice, and guinea pigs can produce brain damage that does not resolve within 90 days. Untreated rats given a dose of 1 × LD_{50} of sarin intramuscularly had brain lesions that were exacerbated over time, up to the end of the experiment at 90 days post-exposure.[143] These brain lesions typically occur from seizures following high doses of nerve agent. In guinea pigs, controlling the seizures after nerve agent exposure stopped almost all the brain lesions regardless of which nerve agent was used (tabun, sarin, soman, cyclosarin, or VX).[144] These brain lesions at high doses of sarin (1 × LD_{50}) can lead to impairments in working and reference memory with no improvement by 6 days after exposure in rats.[145] Some have found that rats given a dose of 1 × LD_{50} or mice given 0.1 × LD_{50} can have minor changes in cardiac measurements, but these effects are mild and cause little to no impairment in the mice or rats.[146,147]

e. Conclusions

Most people who have been exposed to sarin recover completely and have no long-term effects. At doses low enough to not cause seizures, some people can have mild psychological or neurological impairment following exposure, including anxiety, depression, fatigue, weakness, short-term memory problems, and small personality changes, such as increased recklessness. Some of these conditions resolve within a year of the exposure, but some take longer. Most do not directly affect the individual's daily life. Many of these psychological complaints may be related to PTSD from the traumatic nature of peoples' injuries. Thus, it is difficult to determine whether these long-term effects are related to PTSD or to the nerve agents. At higher levels of exposure, brain damage from seizures can occur if treatment is not started quickly enough. This brain damage can lead to much more severe long-term symptoms (e.g., coma, personality changes, and amnesia) that are consistent with brain damage from seizures induced by other factors.

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[143] Tamar Kadar et al., "Sarin-Induced Neuropathy in Rats," *Human and Experimental Toxicology* 14, no. 3 (March 1995): 252–259, https://doi.org/10.1177/096032719501400304.

[144] Tsung-Ming Shih, Steven M. Duniho, and John H. McDonough, "Control of Nerve Agent-Induced Seizures is Critical for Neuroprotection and Survival." *Toxicology and Applied Pharmacology* 188, no. 2 (15 April 2003): 69–80, https://doi.org/10.1016/S0041-008X(03)00019-X.

[145] Ettie Grauer et al., "Single Whole-Body Exposure to Sarin Vapor in Rats: Long-Term Neuronal and Behavioral Deficits," *Toxicology and Applied Pharmacology* 227, no. 2 (1 March 2008): 265–274, https://doi.org/10.1016/j.taap.2007.11.006.

[146] N. Allon et al., "Acute and Long-Lasting Cardiac Changes Following a Single Whole-Body Exposure to Sarin Vapor in Rats," *Toxicological Sciences* 87, no. 2 (1 October 2005): 385–390, https://doi.org/10.1093/toxsci/kfi263.

[147] Mariana Morris, Mary P. Key, and Vera Farha, "Sarin Produces Delayed Cardiac and Central Autonomic Changes," *Experimental Neurology* 203, no. 1 (January 2007): 110–115, https://doi.org/10.1016/j.expneurol.2006.07.027.

2. Tabun (GA)

a. Human exposures

Tabun was used as a chemical warfare agent during the Iran-Iraq War, but little follow-up of nerve agent casualties was done on Iranian veterans, unlike the follow-up of sulfur mustard casualties. One study followed up with 43 Iranian veterans with late complications of sulfur mustard or tabun 22–27 years after exposure.[148] Two of the five soldiers exposed to tabun had a history of seizures and were on anti-epileptic medications. No information was given on the severity of their acute symptoms. No other reports of human exposure to tabun that included a discussion of long-term effects were found.

b. Animal studies

A few animal studies have been performed with tabun, mostly concentrating on whether it can produce delayed neuropathy. Delayed neuropathy following nerve agent exposure has only been observed in animals pretreated with atropine, physostigmine, and oximes and then dosed with 30 or more times the lethal dose of a nerve agent. Delayed neuropathy was not observed in hens given 120–150 × LD_{50} of tabun or in hens given 82 × LD_{50} of tabun.[149,150] This finding indicates that delayed neuropathy may not occur from tabun, even at extremely high doses. Since few studies of tabun were found and all found reported effects in line with other nerve agents, the long-term effects of tabun are assumed to be the same as for other nerve agents. More studies would need to be done, however, to confirm this hypothesis.

3. Soman (GD)

a. Human exposures

Only one report described long-term effects from soman exposure in a human. A 33-year old man splashed soman near his mouth when a syringe broke in his face. He collapsed and had severe acute symptoms. He recovered within a few weeks, but he still

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[148] Emadodin Darchini-Maragheh et al., "Delayed Neurological Complications of Sulphur Mustard and Tabun Poisoning in 43 Iranian Veterans," *Basic & Clinical Pharmacology & Toxicology* 111, no. 6 (December 2012): 426–432, https://onlinelibrary.wiley.com/doi/full/10.1111/j.1742-7843.2012.00922.x.

[149] Gordon et al., "The Delayed Neuropathic Effects."

[150] Jan L. Willems, Marc Nicaise, and Herbert C. De Bisschop, "Delayed Neuropathy by the Organophosphorus Nerve Agents Soman and Tabun," *Archives of Toxicology* 55, no. 1 (March 1984): 76–77, https://link.springer.com/content/pdf/10.1007/BF00316591.pdf.

had problems with cognition 16 days after the accident. He improved considerably when he was retested at 4 and 6 months after exposure.[151]

b. Animal studies

Although reports of human exposure to soman are rare, soman has frequently been used to determine long-term effects of nerve agent exposure in animals. Soman caused delayed neuropathy in one hen of six surviving after being given a dose of 120–150 × LD_{50}.[152] No hens given a soman dose of 38 × LD_{50} developed delayed neuropathy.[153]

Rats, mice, or rhesus monkeys given soman intravenously or subcutaneously can develop brain damage if the dose is high enough to cause the animal to convulse.[154] This brain damage can influence behavior and memory for months after the exposure in mice. Recovery is possible, however. The number of healthy cells did increase for 90 days after injection with 1.2 × LD_{50} soman in mice, indicating that the brain damage was at least partly reversed, even without treatment.[155] The mice also exhibited anxiety-like behavior during unconditioned fear trials at 30 and 90 days after exposure, with worse anxiety symptoms at 30 days after exposure.[156] Another study found anxiety-like behavior in mice given 1.2 × LD_{50} when placed in an open-field apparatus or when given an acoustic startle response test, both of which were unconditioned responses.[157] These studies indicate that the mice may have had some neuronal recovery by 90 days after exposure but still had increased anxiety.

Memory problems outside of emotional distress were also found in mice up to 90 days after exposure to soman, although there was some recovery. One study found that mice that had significant weight loss after soman exposure, which was correlated with brain damage,

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[151] Sidell, "Soman and Sarin."

[152] Willems, Nicaise, and De Bisschop, "Delayed Neuropathy."

[153] Gordon et al., "The Delayed Neuropathic Effects."

[154] Valérie Baille et al., "Acute Exposure to a Low or Mild Dose of Soman: Biochemical, Behavioral and Histopathological Effects," *Pharmacology Biochemistry and Behavior* 69, nos. 3–4 (July 2001): 561–569, https://doi.org/10.1016/S0091-3057(01)00549-4.

[155] Jean-Marc Collombet et al., "Long-Term Consequences of Soman Poisoning in Mice: Part 1. Neuropathology and Neuronal Regeneration in the Amygdala," *Behavioural Brain Research* 191, no. 1 (5 August 2008): 88–94, https://doi.org/10.1016/j.bbr.2008.02.043.

[156] Stéphanie Coubard et al., "Long-Term Consequences of Soman Poisoning in Mice: Part 2. Emotional Behavior," *Behavioural Brain Research* 191, no. 1 (5 August 2008): 95–103. https://doi.org/10.1016/j.bbr.2008.03.027.

[157] Eric M. Prager et al., "LY293558 Prevents Soman-Induced Pathophysiological Alterations in the Basolateral Amygdala and the Development of Anxiety," *Neuropharmacology* 89 (February 2015): 11–18, https://doi.org/10.1016/j.neuropharm.2014.08.014.

had only a slight recovery in learning skills and motor performance by 90 days after exposure.[158] Another study found a recovery of standard emotional behavior in mice by 90 days after exposure to 1.2 × LD_{50} but not memory.[159]

c. Conclusions

Soman can produce memory, emotional, or behavioral effects in mice and humans following severe exposure. In the human, the cognitive problems resolved by 6 months after exposure. Some studies have found that anxiety-like behaviors and memory problems can persist for more than 90 days after exposure in mice, although some responses, such as the conditioned fear response, can resolve by 90 days afterwards. No studies or reports looked at individuals who had been exposed to mild or moderate doses of soman. The responses to severe or very severe doses of soman in humans or animals indicates that the brain damage and consequent anxiety and memory problems are similar to those observed in individuals exposed to other nerve agents. Further research would be needed to determine if there are any long-term effects from mild or moderate acute soman exposure.

4. Cyclosarin (GF)

No studies of animals or humans exposed to cyclosarin at levels great enough to produce acute symptoms were found. One study of Gulf War veterans found that those possibly exposed to low levels of cyclosarin or sarin during the weapons demolitions at Khamisiyah had less proficient neurobehavioral functioning than control subjects, but none of those veterans had acute symptoms of exposure and the very small doses to which they may have been exposed are estimates.[160]

Since there is no information on long-term effects from cyclosarin exposures that produce acute symptoms, the long-term effects of cyclosarin are assumed to be the same as those for other nerve agents, but more studies would need to be done to confirm this hypothesis.

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[158] Pierre Filliat et al., "Long-Term Behavioral Consequences of Soman Poisoning in Mice," *NeuroToxicology* 28, no. 3 (May 2007): 508–519, https://doi.org/10.1016/j.neuro.2006.11.004.

[159] Jean-Marc Collombet et al., "Long-Term Effects of Cytokine Treatment on Cognitive Behavioral Recovery and Neuronal Regeneration in Soman-Poisoned Mice," *Behavioural Brain Research* 221, no. 1 (1 August 2011): 261–270, https://doi.org/10.1016/j.bbr.2011.03.006.

[160] Susan P. Proctor et al., "Effects of Sarin and Cyclosarin Exposure during the 1991 Gulf War on Neurobehavioral Functioning in US Army Veterans," *NeuroToxicology* 27, no. 6 (December 2006): 931–939, https://doi.org/10.1016/j.neuro.2006.08.001.

5. VX

Only one report of a human exposure to VX that included follow-up of long-term effects was found. A 56-year old man was sprayed on the back with VX by Japanese terrorists and arrived at the hospital semi-comatose, indicating he had a very severe acute exposure.[161] He was discharged from the hospital 15 days after exposure and suffered from amnesia and had nerve damage in his right shoulder. After 6 months, his shoulder had recovered, but he still had anterograde and retrograde amnesia.[162] Amnesia was reported in only one individual exposed to sarin, although few of those exposed to sarin had acute symptoms that were as severe as those that this man had.[163]

Due to the chemical makeup of VX, it is unlikely to cause delayed neuropathy, even at high doses, but no animal studies were found that confirmed this finding or that tested other long-term effects of VX.[164] The long-term effects of VX are assumed to be similar to those for other nerve agents, but more studies would need to be done to confirm this hypothesis.

6. Conclusions (Nerve Agents)

Conclusion: Most of the information on the long-term effects of nerve agents comes from exposures to sarin, although a few studies have been done or exposures have been recorded for tabun, soman, cyclosarin, and VX. Across all nerve agents, most people recover completely from mild, moderate, or severe acute doses that are not accompanied by acute seizures. Some people report mild psychological or neurological problems for months after the acute illness, including anxiety, depression, memory problems, fatigue, or weakness. PTSD following the exposure is common, especially in situations like the Tokyo sarin attack, which are traumatic. This mix of reactions makes it difficult to determine whether the psychological symptoms are from the nerve agent itself or PTSD from a traumatic experience. In some people, mild psychological concerns can resolve within the first year, while the concerns linger in others. Very severe acute doses of nerve agent—those leading to acute seizures/convulsions—can lead to brain damage and consequently worse neurological effects. Some people exposed to high levels of sarin, tabun, soman, or VX have experienced amnesia, epilepsy, coma, personality changes, or other major cognitive impairments. Some of these conditions can resolve over time, while others appear to linger.

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[161] H. Nozaki et al., "A Case of VX Poisoning and the Difference from Sarin," *The Lancet* 346, no. 8976 (9 September 1995): 698–699, https://doi.org/10.1016/S0140-6736(95)92306-3.

[162] Ibid.

[163] Hatta et al. "Amnesia from Sarin Poisoning."

[164] Munro, Ambrose, and Watson, "Toxicity of the Organophosphate Warfare Agents."

Caveats:

- **Although some studies and reports were found of people or animals being exposed to tabun, soman, and VX, not enough were available to determine whether the long-term effects of each nerve agent were the same. In addition, most of the reported cases of tabun, soman, and VX exposure were very severe doses, while most of the reported cases of sarin exposure were mild or moderate doses, further complicating the comparison. No studies or reports were available on people exposed to cyclosarin in meaningful doses.**
- **Many of the long-term symptoms of nerve agent exposure are mild psychological symptoms. Many of the people who are exposed to nerve agents develop PTSD as a result of the traumatic experience, and it is often difficult to determine whether the symptoms are the result of the trauma or the nerve agent.**
- **Many animal exposures were based on intramuscular or IV exposures rather than aerosol exposures.**
- **Although minimal data are available on sequelae after acute nerve agent exposure that causes seizures/convulsions, it is reasonable to assume that the sequelae would be the same as from seizures/convulsions due to any other cause.**

B. Sulfur Mustard (HD)

Following World War I and the Iran-Iraq War, sulfur mustard caused some of the most debilitating long-term effects from chemical agents among veterans. In addition, sulfur mustard was tested on U.S. military personnel during World War II, and concerns about potential long-term health consequences of that testing led to a large study in 1993 by the Veterans Administration on the health effects of sulfur mustard.[165] The most common and most debilitating chronic effect is chronic bronchitis and associated chronic respiratory conditions. Chronic skin defects and ocular conditions have also been reported, and controversy exists over the potential for sulfur mustard to cause increased rates of infertility in men and cancer. Although the long-term effects are often more severe or more frequent in people who had more severe acute exposures, individuals can still have substantial long-term effects after mild or moderate initial exposures.[166]

Chronic bronchitis following inhalational sulfur mustard exposure has been extensively studied, especially among Iranian veterans following the Iran-Iraq War. Unfortunately, many of the studies on chronic bronchitis follow the same small groups (<100 people) over time and do not record the severity of initial illness or only focus on those with severe acute or chronic injury. Other studies do not separate the type of respiratory symptoms or use categories that are not replicated by other studies. Therefore, although the studies could not be combined or compared effectively, they do provide an overall indication

[165] Institute of Medicine, *Veterans at Risk: The Health Effects of Mustard Gas and Lewisite* (Washington, DC: The National Academies Press, 1993), https://doi.org/10.17226/2058.

[166] M. Ghanei et al., "Late Respiratory Effects of Sulfur Mustard: How Is the Early Symptoms Severity Involved?" *Chronic Respiratory Disease* 5, no. 2 (2008): 95–100, https://journals.sagepub.com/doi/pdf/10.1177/1479972307087191.

of how frequent chronic lung effects can occur from sulfur mustard. Most studies did not look at smokers or noted that veterans who had been exposed to sulfur mustard were less likely to smoke or smoked less frequently than unexposed veterans.[167]

Among those with severe initial exposures to sulfur mustard, chronic bronchitis and other chronic lung conditions are common. Emad and Reza Rezaian[168] looked at 197 former patients of Shiraz University Hospital 10 years after severe sulfur mustard exposure. Of these 197 patients, 21 (10.7%) had asthma, 116 (59.9%) had chronic bronchitis, 19 (9.6%) had airway narrowing, and 24 (12.2%) had pulmonary fibrosis. In contrast, a control group of 86 non-exposed veterans had no chronic lung conditions except for one (1.1%) individual with chronic bronchitis. Among 40 Iranian veterans severely exposed at Khorasan, all had coughing, and 34 (85%) had difficulty breathing 16–20 years after exposure.[169] Two (5%) patients were diagnosed with simple chronic bronchitis, 10 (25%) with asthma, 14 (35%) with Chronic Obstructive Pulmonary Disease (COPD), 13 (32.5%) with bronchiectasis, 6 (15%) with large airway narrowing, and 3 (7.5%) with pulmonary fibrosis. Among 34,000 Iranian soldiers exposed to sulfur mustard, 14,450 (42.5%) had chronic lung lesions 13–20 years after exposure.[170] Mild lesions were found in 12,580 (37%), moderate lesions in 1,530 (4.5%), and severe lesions in 3,400 (1%). This study did not include information about chronic symptoms or diagnoses such as bronchitis nor did it specify the severity of acute illness. A study of the medical records of 1,337 people in Tehran previously treated for acute sulfur mustard injuries found that 432 (31.6%) were diagnosed with at least one type of lung lesion years after exposure.[171] Most commonly, people presented with lung lesions 6–9 years after initial exposure. The study did not specify the types of lung lesions or severity.

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[167] Mohammad Reza Zafarghandi et al., "Incidence of Cancer in Iranian Sulfur Mustard Exposed Veterans: A Long-Term Follow-Up Cohort Study," *Cancer Causes & Control* 24, no. 1 (January 2013): 99–105, https://link.springer.com/article/10.1007%2Fs10552-012-0094-8.

[168] Ali Emad and Gholam Reza Rezaian, "The Diversity of the Effects of Sulfur Mustard Gas Inhalation on Respiratory System 10 Years after a Single, Heavy Exposure: Analysis of 197 Cases," *Chest* 112, no. 3 (September 1997): 734–738, https://doi.org/10.1378/chest.112.3.734.

[169] Mahdi Balali-Mood et al., "Long-Term Complications of Sulphur Mustard Poisoning in Severely Intoxicated Iranian Veterans," *Fundamental and Clinical Pharmacology* 19, no. 6 (December 2005): 713–721, https://doi.org/10.1111/j.1472-8206.2005.00364.x.

[170] Shahriar Khateri et al., "Incidence of Lung, Eye, and Skin Lesions as Late Complications in 34,000 Iranians with Wartime Exposure to Mustard Agent," *Journal of Occupational & Environmental Medicine* 45, no. 11 (November 2003): 1136–1143, doi:10.1097/01.jom.0000094993.20914.d1.

[171] Karimi Zarchi, Ali Akbar, and Kourosh Holakouie Naieni, "Long-Term Pulmonary Complications in Combatants Exposed to Mustard Gas: A Historical Cohort Study," *International Journal of Epidemiology* 33, no. 3 (2004): 579–581, https://www.researchgate.net/publication/8542122_Long-term_pulmonary_complications_in_combatants_exposed_to_mustard_gas_A_historical_cohort_study.

Individuals with any level of exposure to sulfur mustard can later present with chronic lung symptoms, and the chronic effects can be just as debilitating in those with mild or moderate acute exposures as in those with severe acute exposures. In a study of 15 people with chronic lung disease from sulfur mustard, the 6 people with mild acute exposures had no difference in their symptoms of cough or difficulty breathing or diagnosis of bronchiolitis or bronchiolectasis (half were diagnosed) compared to the 9 people with severe acute exposures.[172] In a larger study of Iranians with chronic lung symptoms, no difference was found in frequency of cough or trouble breathing among 115 people with sulfur mustard exposure but no acute symptoms, among 273 people with acute symptoms but no hospitalization (mild-to-moderate exposure), or among 215 people with acute symptoms severe enough to require hospitalization (severe exposure).[173] Those with acute symptoms of sulfur mustard exposure, however, were more likely to have obstructions in their lung and were prone to wheezing.

Symptoms of chronic bronchitis tend to get worse over time rather than better and can begin years after the acute exposure.[174,175] Because of these chronic lung effects, the quality of life can decrease substantially.[176] Individuals often report that they cannot work in their same jobs, visit friends, or take part in other daily activities without being easily fatigued or unable to breathe. Civilians who were exposed to sulfur mustard reported higher levels of obsessive-compulsive disorder, depression, anxiety, and hostility than those of unexposed civilians.[177] These conditions may be due to other chronic effects of sulfur mustard or may be a result of the initial trauma as opposed to an independent effect of sulfur mustard.

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[172] Mostafa Ghanei et al., "An International Collaborative Pathologic Study of Surgical Lung Biopsies from Mustard-Gas Exposed Patients," *Respiratory Medicine* 102, no. 6 (June 2008): 825–830, https://doi.org/10.1016/j.rmed.2008.01.016.

[173] Ghanei et al., "Late Respiratory Effects of Sulfur Mustard."

[174] Mahdi Balali-Mood et al., "Delayed Toxic Effects of Sulfur Mustard on Respiratory Tract of Iranian Veterans," *Human and Experimental Toxicology* 30, no. 9 (September 2011): 1141–1149, https://doi.org/10.1177/0960327110389501.

[175] Zarchi, Akbar, and Naieni, "Long-Term Pulmonary Complications."

[176] Soheil Najafi Mehri et al., "Experiences Living with Fatigue in Iranian Veterans Chemically Injured by Sulfur Mustard Gas: A Phenomenological Study," *Asian Nursing Research* 6, no. 4 (December 2012): 181–186, https://doi.org/10.1016/j.anr.2012.10.008.

[177] Rasoul Roshan et al., "Long-Term Effects of Sulfur Mustard on Civilians' Mental Health 20 Years after Exposure (The Sardasht-Iran Cohort Study)," *Health and Quality of Life Outcomes* 11 (April 24, 2013): 69, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3641015/.

The link between inhalational sulfur mustard exposure and lung cancer has been studied among Iran-Iraq veterans and among those exposed during World War I or World War II. Chronic exposures to sulfur mustard was correlated to lung cancer among factory workers in World War II.[178,179] A link between a single exposure to sulfur mustard and cancer, however, has been more difficult to deduce. Among British veterans who had pensions resulting from sulfur mustard poisoning in World War I, their rate of mortality was higher than that expected from mortality tables.[180] They also had higher death rates than those expected from lung cancer but not from other kinds of cancer. A study of the mortality of U.S. World War I veterans found a slightly higher risk of death from lung cancer or pneumonia among the 2,718 hospitalized for acute sulfur mustard poisoning than among the 1,885 who had acute pneumonia from Spanish flu or among the 2,578 who had wounds of the extremities.[181] Iranian veterans exposed to sulfur mustard had a higher risk (factor of 1.64 higher) of cancers, especially hematological and gastrointestinal cancers, but not lung cancer.[182] The study did not include information on the veterans' routes of exposure. The risk of cancer for non-smokers exposed to sulfur mustard was approximately the same as that for smokers who had not been exposed to sulfur mustard. Those exposed to sulfur mustard, however, were not more likely to smoke, and there has not been any evidence suggesting that smoking and sulfur mustard may work synergistically to increase cancer risk.[183] Other papers did not find statistically significant higher risks of cancer with sulfur mustard exposure.[184] Low levels of exposure, such as those in U.S. Navy veterans who took part in sulfur mustard tests, were not related to increases in mortality.[185]

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[178] Sunao Wada et al., "Mustard Gas as a Cause of Respiratory Neoplasia in Man," *The Lancet* 291, no. 7553 (1 June 1968): 1161–1163, https://doi.org/10.1016/S0140-6736(68)91863-1.

[179] Institute of Medicine. *Veterans at Risk.*

[180] R. A. M. Case and A. J. Lea, "Mustard Gas Poisoning, Chronic Bronchitis, and Lung Cancer: An Investigation into the Possibility That Poisoning by Mustard Gas in the 1914-18 War Might Be a Factor in the Production of Neoplasia," *British Journal of Preventive and Social Medicine* 9, no. 2 (April 1955): 62–72, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1058579/.

[181] Gilbert W. Beebe, "Lung Cancer in World War I Veterans: Possible Relation to Mustard-Gas Injury and 1918 Influenza Epidemic," *Journal of the National Cancer Institute* 25 (December 1960): 1231–1252, https://doi.org/10.1093/jnci/25.6.1231.

[182] Zafarghandi et al., "Incidence of Cancer in Iranian Sulfur Mustard Exposed Veterans."

[183] Annetta P. Watson, Troyce D. Jones, and Guy D. Griffin, ""Sulfur Mustard as a Carcinogen: Application of Relative Potency Analysis to the Chemical Warfare Agents H, HD, and HT," *Regulatory Toxicology and Pharmacology* 10, no. 1 (August 1989): 1–25, https://doi.org/10.1016/0273-2300(89)90010-X.

[184] Mostafa Ghanei and Ali Amini Harandi, "Lung Carcinogenicity of Sulfur Mustard," *Clinical Lung Cancer* 11, no. 1 (January 2010): 13–17, https://doi.org/10.3816/CLC.2010.n.002.

[185] Tim Bullman and Han Kang, "A Fifty Year Mortality Follow-Up Study of Veterans Exposed to Low Level Chemical Warfare Agent, Mustard Gas," *Annals of Epidemiology* 10, no. 5 (July 2000): 333–338, https://doi.org/10.1016/S1047-2797(00)00060-0.

Skin lesions, hyper- or hypo-pigmentation, or other skin conditions are common following cutaneous sulfur mustard exposure. Among 34,000 Iranian soldiers exposed to sulfur mustard, 8,330 (24.5%) had skin lesions, 7,820 (23%) had mild skin lesions, and 5,100 (1.5%) had moderate skin lesions.[186] Most of these lesions were hyper- or hypo-pigmentation. An 800 person subset of the 34,000 soldiers with skin lesions was examined more closely 14–20 years after exposure.[187] Almost all these soldiers (747 (93.4%)) had non-specific skin disorders, such as dermatitis, eczema, and so forth, 440 (5.5%) had sulfur mustard scars, and 88 (1.1%) had malignant skin cancer, significantly higher than the results of the National Health Survey of Iran. In 40 Iranians with severe acute sulfur mustard exposure, 26 (65%) had itching and 8 (20%) had burning. The most common outward signs were hyper-pigmentation (22 (55%)), rash (17 (42.5%)), and dry skin (16 (40%)).[188] Iranian civilians who were exposed to sulfur mustard were more likely to report itching, burning, dry skin, hyper-pigmentation, and cherry angiomas than Iranian civilians who were not exposed.[189] Overall, 84.5% of the civilians who were hospitalized from their sulfur mustard injuries had skin lesions, compared to 69.6% of the civilians who were exposed but not hospitalized and 55.5% of the unexposed civilians. When comparing 154 Iranians exposed to sulfur mustard to 175 Iranians exposed to nerve agents 20 years previously, those exposed to sulfur mustard had significantly more dry skin (75 (48.7%) vs. 32 (18.3%)), itching (45 (29.2%) vs. 33 (18.8%)), and burning (6 (3.8%) vs. 9 (0.5%)) than those exposed to nerve agents.[190] The nerve agent patients had higher rates of acne, likely due to their higher incidence of psychological sequelae. With severe burns, nerve damage can occur. Five people exposed in Iran and five people exposed in the Faroe Islands from discarded mustard shells had neuropathic pain (100%), short-term memory impairment (80%), and intermittent cold/warm feelings (50%).[191] These conditions were due to the nerve damage from acute sulfur mustard burns 8–13 years before.

Chronic ocular effects of sulfur mustard are less common but can be severe and can lead to decreases in vision. In more than 5,000 people with acute sulfur mustard exposure

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[186] Khateri et al., "Incidence of Lung, Eye, and Skin Lesions."

[187] Emadi, Mortazavi, and Mortazavi, "Late Cutaneous Manifestations 14 to 20 Years after Wartime Exposure."

[188] Mahdi Balali-Mood et al., "Long-Term Complications of Sulphur Mustard Poisoning."

[189] Athar Moin et al., "Long-Term Skin Findings of Sulfur Mustard Exposure on the Civilians of Sardasht, Iran," *Toxin Reviews* 28, no. 1 (2009): 24–29, http://www.tandfonline.com/doi/abs/10.1080/15569540802689311.

[190] Seyed Naser Emadi et al., "Comparison Late Cutaneous Complications between Exposure to Sulfur Mustard and Nerve Agents," *Cutaneous and Ocular Toxicology* 31, no. 3 (September 2012): 214–219, https://www.ncbi.nlm.nih.gov/pubmed/22187952.gg.

[191] Annemarie B. Thomsen, Jørgen Eriksen, and Knud Smidt-Nielsen, "Chronic Neuropathic Symptoms after Exposure to Mustard Gas: A Long-Term Investigation," *Journal of the American Academy of Dermatology* 39, no. 2 (August 1998): 187–190, https://doi.org/10.1016/S0190-9622(98)70072-6.

in the Iran-Iraq War, 90% fully recovered from their ocular injuries after several months, but 10% did not.[192] The study did not specify the sequelae in the 10% who did not fully recover. Among 34,000 Iranians exposed to sulfur mustard, 11,900 (35%) had mild eye lesions, 1,156 (3.6%) had moderate eye lesions, and 238 (0.7%) had severe eye lesions.[193] Among 40 Iranian veterans with severe sulfur mustard exposure, 17 (42.5%) had eye itching, 15 (37.5%) had eye burning, 12 (30%) had photophobia, and 11 (27.5%) had tearing 16–20 years after exposure.[194] One of the most debilitating ocular sequelae from sulfur mustard is keratitis, which is an inflammation of the cornea. Keratitis can begin immediately after the acute exposure or can have a delayed onset. In 48 Iranian patients with keratitis from mustard gas, 31 (64.6%) had chronic keratitis starting immediately after the acute exposure, and 17 (35.4%) had keratitis that went away after the initial exposure and returned 1 to 15 years later.[195] These individuals had corneal scars or opacity and subsequent vision loss and ocular irritation. The Iranians were young adults when exposed, so this vision loss and ocular irritation was likely not due to age-related decreases in vision. Occasionally, some people have reported blindness following sulfur mustard injury.[196] Severe long-term eye effects can be correlated to severe long-term respiratory effects, since severe exposure to the eyes commonly accompanies severe exposure to the respiratory system. Of 112 Iranian veterans exposed to sulfur mustard, 79 (70.6%) had objective ocular problems and 94 (83.9%) had subjective ocular problems.[197] In addition, they were separated out by those who had no respiratory impairment (42 (37.5%) people), mild respiratory impairment (25 people), or moderate to severe respiratory impairment (45 (22%) people). Of those with respiratory impairment, 65 (93%) had ocular problems, while only 14 (33%) of those with no respiratory impairment had ocular problems. The ocular problems were more severe in the moderate-to-severe respiratory group, including delayed keratitis in 10 (22.2%) patients and moderate to severe conjunctival vascular tortuosity in 25 (55.5%) patients. Those with mild respiratory impairment had milder ocular symptoms, including mild to moderate conjunctival vascular tortuosity in 18 (82%) patients.

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[192] M. R. Safarinejad, S. A. Moosavi, and B. Montazeri, "Ocular Injuries Caused by Mustard Gas: Diagnosis, Treatment, and Medical Defense," *Military Medicine* 166, no. 1 (January 2001): 67–70, https://www.ncbi.nlm.nih.gov/pubmed/11197102.

[193] Khateri et al., "Incidence of Lung, Eye, and Skin Lesions.

[194] Balali-Mood et al., "Long-Term Complications of Sulphur Mustard Poisoning."

[195] Mohammad-Ali Javadi et al., "Chronic and Delayed-Onset Mustard Gas Keratitia: Report of 48 Patients and Rview of Literature," *Ophthalmology* 112, no. 4 (April 2005): 617–625.e2, https://doi.org/10.1016/j.ophtha.2004.09.027.

[196] Institute of Medicine. *Veterans at Risk.*

[197] Mohammad Reza Sedghipour et al., "The Ocular Complications of Mustard Gas Poisoning and Their Association with the Respiratory System Involvement: An Experience in 112 Iranian Veterans," *Cutaneous and Ocular Toxicology* 31, no. 1 (March 2012): 48–52, https://www.ncbi.nlm.nih.gov/pubmed/22053994.

Some have suggested that sperm count and fertility can be affected by prior sulfur mustard exposure. The evidence for this assertion, however, has been mixed. Some studies have found lower levels of testosterone, androgen, and libido in those previously exposed to sulfur mustard.[198] Infertile couples exposed to sulfur mustard had problems with sperm production years after exposure, although that study had no control group of infertile couples who had not been exposed to sulfur mustard.[199] A different study, however, found no difference in fertility between civilian couples exposed to sulfur mustard and couples not exposed.[200] Therefore, until more studies have been done, a link between sulfur mustard and fertility cannot be determined.

Sulfur mustard primarily damages the eyes, skin, and lungs, and substantial chronic effects of sulfur mustard have been found for all three areas. Chronic bronchitis and other lung-related illnesses can be the most debilitating long-term effects. The lung symptoms tend to worsen over time (starting a few years after exposure) and can lead to chronic cough, trouble breathing, fatigue, and psychological symptoms such as depression. Lung cancer risk was increased in some sulfur mustard exposed veterans in World War I, although a definitive link between single exposure to sulfur mustard and increased cancer has not yet been determined. Skin lesions are common chronic complaints from sulfur mustard, and those exposed to sulfur mustard tend to have more dry skin, itching, and burning sensations than those not exposed. Ocular complications are less common but can include corneal and vein problems, which can lead to loss of vision. Some effects, such as lung symptoms and ocular problems, can arise years after the initial exposure, so careful monitoring of veterans in the long term may be required.

Conclusion: Sulfur mustard has been associated with substantial debilitating long-term effects in those exposed to it, even at low doses. Chronic lung effects are often the most severe and can occur even after mild acute exposures, occurring in approximately ~30%–50% of exposed individuals (no information relative rate based on exposure severity). These effects include chronic bronchitis, asthma, and other lung disorders, which lead to cough, trouble breathing, and other lung symptoms. The effects worsen over time and can start 5–10 years after the acute exposure. Some studies have found an increased risk of lung cancer among those exposed to sulfur mustard, although not all studies have confirmed this finding, and the risk has been more prominent in those with chronic exposures to sulfur mustard than in those with a single acute exposure. Those who have been exposed to sulfur mustard have increased skin lesions, mostly

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[198] Eisa Tahmasbpour Marzony, Mostafa Ghanei, and Yunes Panahi, "Relationship of Oxidative Stress with Male Infertility in Sulfur Mustard-Exposed Injuries," *Asian Pacific Journal of Reproduction* 5, no. 1 (March 2016): 1–9, https://doi.org/10.1016/j.apjr.2015.12.001.

[199] M. R. Safarinejad, "Testicular Effects of Mustard Gas," *Urology* 58, no. 1 (July 2001): 90–94, https://doi.org/10.1016/S0090-4295(01)01085-8.

[200] Mostafa Ghanei et al., "Assessment of Fertility among Mustard-Exposed Residents of Sardasht, Iran: A Historical Cohort Study," *Reproductive Toxicology* 18, no. 5 (July 2004): 635–639, https://doi.org/10.1016/j.reprotox.2004.03.003.

mild. Chronic symptoms include increased dry skin (~40%–48% of individuals), itching (~30% of individuals), and burning (3.8%–20% of individuals). Ocular symptoms occur less frequently (~10% or less of individuals) but can include vein problems, corneal scars, or opacity, all of which can lead to loss of vision. Corneal scarring can start immediately after exposure or can start up to 20 years after exposure. Ocular injuries tend to be more severe in individuals with moderate or severe chronic respiratory conditions, indicating that although those with mild acute injuries can have chronic effects, these effects may be more pronounced in those with moderate or severe acute injuries. All these long-term effects tend to worsen or stay the same over time, and almost all can only be treated with supportive care.

Caveats:

- **Although there may be an increased risk of lung or other cancers from sulfur mustard exposure, the risk increase may be small and difficult to detect.**
- **No studies gave the acute dose, and very few gave the severity of acute symptoms.**
- **Many studies did not include unexposed control groups or only looked at those people with severe acute or long-term symptoms, which may affect the risk estimate for mild and severe long-term effects.**

C. Chlorine (Cl_2)

Most individuals exposed to chlorine recover completely from their acute respiratory symptoms, although, in some instances, people can have respiratory difficulties for years following exposure. Table 7 provides a list of studies that determined the persistence of sequelae (long-term effects) from chlorine and the rate of sequelae among those exposed to chlorine. The most common respiratory difficulty described is Reactive Airways Dysfunction Syndrome (RADS), which can produce asthma and lung dysfunction following exposure to an irritant such as chlorine.[201] This condition is diagnosed via spirometry, which determines how much an individual inhales and exhales and how quickly he or she exhales. Almost all the studies in Table 7 used spirometry to diagnose sequelae. One exception is Duncan's study, which used a mailed questionnaire to determine long-term symptoms.[202] This self-reporting method may explain why the rate of sequelae was much higher in that study than in others since the self-reported symptoms were not corroborated with spirometry results. There was also a high rate of post-traumatic stress in the cohort, which was correlated to decreases in lung capacity or respiratory symptoms.[203] Sequelae

[201] Gary W. Hoyle and Erik R. Svendsen, "Persistent Effects of Chlorine Inhalation on Respiratory Health," *Annals of the New York Academy of Sciences* 1378, no. 1 (August 2016): 33–40, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5063681/.

[202] Mary Anne Duncan et al., "Follow-Up Assessment of Health Consequences after a Chlorine Release from a Train Derailment—Graniteville, SC, 2005," *Journal of Medical Toxicology* 7, no. 1 (March 2011): 85–91, doi:10.1007/s13181-010-0130-6.

[203] Jay P. Ginsberg et al., "Posttraumatic Stress and Tendency to Panic in the Aftermath of the Chlorine Gas Disaster in Graniteville, South Carolina," *Social Psychiatry and Psychiatric Epidemiology* 47, no. 9 (September 2012): 1441–1448, doi:10.1007/s00127-011-0449-6.

could occur after moderate or severe initial exposure, although it was more common in those with more severe initial symptoms (see Table 7).

Smoking and history of asthma or respiratory illness have been associated with development of RADS following chlorine exposure.[204] When provided in studies, smoking status is included in Table 7. Although smokers were sometimes more likely to develop RADS following chlorine exposure, nonsmokers also developed RADS.[205] Most studies did not have enough smokers and nonsmokers to compare, although one study found that smokers had a greater decrease in lung capacity over time following chlorine exposure than nonsmokers, possibly due to the smoking and the chlorine.[206] Treatment of acute symptoms with corticosteroids or other methods may decrease the prevalence of RADS, although this finding is mostly based on case reports[207] and animal studies.[208]

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[204] David A. Salisbury et al., "First-Aid Reports of Acute Chlorine Gassing among Pulpmill Workers as Predictors of Lung Health Consequences," *American Journal of Industrial Medicine* 20, no. 1 (1991): 71–81, https://www.ncbi.nlm.nih.gov/pubmed/1867219.

[205] Nirmal Charan et al., "Effects of Accidental Chlorine Inhalation on Pulmonary Function." *Western Journal of Medicine* 143, no. 3 (September 1985): 333–336. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1306316/.

[206] Salisbury et al., "First-Aid Reports of Acute Chlorine Gassing."

[207] Edward H. Chester et al., "Pulmonary Injury Following Exposure to Chlorine Gas," *Chest* 72, no. 2 (August 1977): 247–250, https://doi.org/10.1378/chest.72.2.247.

[208] R. Demnati et al., "Effects of Dexamethasone on Functional and Pathological Changes in Rat Brochi Caused by High Acute Exposure to Chlorine," *Toxicological Sciences* 45, no. 2 (October 1998): 242–246, https://doi.org/10.1006/toxs.1998.2532.

Table 7. Rate of Sequelae among Those Exposed to Chlorine

Total # Injured	Total # Sequelae	# Smokers/ Prior Asthma	# Smokers w/ Sequelae	Time to Resolution	Acute Symptom Severity	Type of Accident	Source
2	1 (50%)	2 (100%)	1 (50%)	>55 months	Severe	Industrial	Chester (1977)[209]
12	0 (0%)	3 (25%)	0 (0%)	1 week	Mild	Chlorine Tank	Hasan (1983)[210]
6	0 (0%)	6 (100%)	0 (0%)	5 months	Moderate	Chlorine Tank	Hasan (1983)
129	0 (0%)	Unknown	0 (0%)	<1 month	Unknown	Unknown	Barret (1984)[211]
13	5 (45.5%)	11 (85%)	2/3 (66%) in >2 years group	1–2 years: 2, 2–9 years: 0[a] 9–12 years: 2 >12 years: 5	Severe	Industrial	Charan (1985)[212], Schwartz (1990)[213]
191	68 (35.6%)	Unknown	Unknown	>3 years	Unknown	World War I	Jones (1986)[214]
29	0 (0%)	Unknown	Unknown	<16 months	Unknown	Industrial	Jones (1986)[b]
12	0 (0%)	Unknown	Unknown	<7 years	Unknown	Industrial	Jones (1986)

[209] Edward H. Chester et al., "Pulmonary Injury."

[210] Faysal M. Hasan, Adel Gehshan, and Farid J. D. Fuleihan, "Resolution of Pulmonary Dysfunction Following Acute Chlorine Exposure," *Archives of Environmental Health* 38, no. 2 (March–April 1983): 76–80, https://doi.org/10.1080/00039896.1983.10543984.

[211] L. Barret and J. Faure, "Chlorine Poisoning," *The Lancet* 323, no. 8376 (10 March 1984): 561–562, https://www.sciencedirect.com/science/article/pii/S0140673684909528.

[212] Charan et al., "Effects of Accidental Chlorine Inhalation."

[213] David A. Schwartz, Dorsett D. Smith, and Sambasiva Lakshminarayan, "The Pulmonary Sequelae Associated with Accidental Inhalation of Chlorine Gas," *Chest* 97, no. 4 (April 1990): 820–825, https://doi.org/10.1378/chest.97.4.820.

[214] Robert N. Jones et al., "Lung Function after Acute Chlorine Exposure," *American Review of Respiratory Disease* 134, no. 5 (November 1, 1986): 1190–1195, https://www.ncbi.nlm.nih.gov/pubmed/3789518.

Total # Injured	Total # Sequelae	# Smokers/ Prior Asthma	# Smokers w/ Sequelae	Time to Resolution	Acute Symptom Severity	Type of Accident	Source
3	0 (0%)	Unknown	0 (100%)	1 hour	Moderate	Pool	Vinsel (1990)[215]
1	1 (100%)	1 (100%)	1 (100%)	>4 years	Severe	Gas Leak	Moore (1991)[216]
16	0 (0%)	Unknown	Unknown	<3 months	Severe	Industrial	Moullick (1992)[217]
1	1 (100%)	0 (0%)	0 (0%)	>2 years	Severe	Cleaner	Deschamps (1994)[218]
1	1 (100%)	0 (0%)	0 (0%)	5 months	Moderate	Industrial	Lemière (1997)[219]
1	1 (100%)	0 (0%)	0 (0%)	5 months	Severe	Pool	Parimon (2004)[220]
1	0 (100%)	0 (0%)	0 (0%)	6 days	Severe	Cleaner	Akdur (2006)[221]
52	0 (0%)	Unknown	Unknown	6 hours	Moderate	Pool	Mohan (2010)[222]

[215] Paul J. Vinsel, "Treatment of Acute Chlorine Gas Inhalation with Nebulized Sodium Bicarbonate," *The Journal of Emergency Medicine* 8, no. 3 (May–June 1990): 327–329, https://doi.org/10.1016/0736-4679(90)90014-M.

[216] Brad B. Moore and Michael Sherman, "Chronic Reactive Airway Disease Following Acute Chlorine Gas Exposure in an Asymptomatic Patient," *Chest* 100, no. 3 (September 1991): 855–856, https://doi.org/10.1378/chest.100.3.855.

[217] N. D. Moulick et al., "Acute Accidental Exposure to Chlorine Fumes--A Study of 82 Cases," *Indian Journal of Chest Disease and Allied Sciences* 34, no. 2 (April 1992): 85–89, https://europepmc.org/abstract/med/1459667.

[218] Dominique Deschamps et al., "Persistent Asthma after Inhalation of a Mixture of Sodium Hypochlorite and Hydrochloric Acid," *Chest* 105, no. 6 (June 1994): 1895–1896, https://doi.org/10.1378/chest.105.6.1895.

[219] C. Lemière, J.-L. Malo, and M. Boutet, "Reactive Airways Dysfunction Syndrome Due to Chlorine: Sequential Bronchial Biopsies and Functional Assessment," *European Respiratory Journal* 10, no. 1 (January 1997): 241–244, https://pdfs.semanticscholar.org/4ff3/1d4206ec301e55f3623b69797dcc571ef097.pdf.

[220] Tanyalak Parimon, Jeffrey P. Kane, and David J. Pierson, "Acute Inhalation Injury with Evidence of Diffuse Bronchitis Following Chlorine Gas Exposure at a Swimming Pool," *Respiratory Care* 49, no. 3 (March 2004): 291–294, https://www.ncbi.nlm.nih.gov/pubmed/14982650.

[221] O. Akdur et al., "A Rare Complication of Chlorine Gas Inhalation: Pneumomediastinum," *Emergency Medicine Journal* 23, no. 11 (November 2006): e59, doi:10.1136/emj.2006.040022.

[222] Alladi Mohan et al., "Acute Accidental Exposure to Chlorine Gas: Clinical Presentation, Pulmonary Functions and Outcomes," *Indian Journal of Chest Disease and Allied Sciences* 52, no. 3 (July–September 2010): 149–152, https://www.ncbi.nlm.nih.gov/pubmed/20949733.

Total # Injured	Total # Sequelae	# Smokers/ Prior Asthma	# Smokers w/ Sequelae	Time to Resolution	Acute Symptom Severity	Type of Accident	Source
12	3 (25%)	0 (0%)	0 (0%)	6 months	Severe	Pool	Mohan (2010)
94	50 (53%)	Unknown	Unknown	>5 months	Moderate-Severe	Train	Duncan (2011)[223]
78	6 (7.7%)	Unknown	Unknown	<4 months	Unknown	Industrial	Whitlow (2012)[224]
1	1 (100%)	0 (0%)	0 (0%)	1 year	Severe	Cleaner	Hasan (2014)[225]

[a] Charan measures the same subjects at 1 and 2 years after exposure that Schwartz measured at 9 and 12 years after exposure. Charan states that three individuals had abnormal lung spirometry 2 years after exposure, but Schwartz states that an additional four people (seven total) had abnormal lung spirometry 9 years after exposure and five total had abnormal lung spirometry 12 years after exposure. Most of these individuals were smokers or ex-smokers.

[b] Jones included a literature review of previous studies. Many were unavailable to us otherwise.

[223] Duncan et al., "Follow-Up Assessment of Health Consequences."

[224] Ashley Whitlow et al., "Chlorine Gas Release Associated with Employee Language Barrier – Arkansas, 2011," *Morbidity and Mortality Weekly Report* (MMWR) 61, no. 48 (December 7, 2012): 981–985, https://www.cdc.gov/mmwr/pdf/wk/mm6148.pdf.

[225] Naveed Hasan and Michael L. Scharf, "Acute Respiratory Distress Syndrome Secondary to Household Use of Chlorine-Based Bleach: Brief Report and Review of Literature," *Materia Socio Medica* 26, no. 3 (June 2014): 211–213, https://search.proquest.com/docview/1540742048?pq-origsite=gscholar.

In most people, the effects of chlorine resolve within a few hours to a few weeks. In some, however, RADS can develop and the individual can have symptoms for a few months to a few years. In rare occasions, RADS can last more than 4 years. This pathology of speedy recovery in most but a slow recovery in some has also been observed in rats.[226] RADS can develop after moderate or severe exposure, although it is more common among those with severe exposures. There is limited evidence that smokers or people with a history of asthma are more likely to develop RADS.

Conclusion: In most individuals, the effects of chlorine resolve on their own within the first few weeks. In some (~30%), symptoms can take up to 6 months to resolve. In a few (mostly from case reports, so rate cannot be determined), symptoms can last for up to 5 years. Most individuals with sequelae from chlorine have RADS, which is characterized by asthma and decreases in lung capacity following exposure to an irritant, such as chlorine. Some studies have indicated that smoking and a previous history of asthma can increase the probability of developing RADS after chlorine exposure, while prompt acute treatment can decrease the probability, but that has mostly been described in case reports or small groups rather than in any large studies.

Caveats:

- **Many of the papers describing RADS that lasted longer than 1 year are case reports, so rate could not be determined.**
- **One study indicated that those with post-traumatic stress were more likely to report respiratory symptoms following chlorine exposure, indicating that there may be a psychological component to the symptoms.**
- **Most of the papers describing the relationship between smoking status and RADS following chlorine exposure were based on small sample sizes.**

[226] R. Demnati et al., "Time-Course of Functional and Pathological Changes after a Single High Acute Inhalation of Chlorine in Rats," *European Respiratory Journal* 11, no. 4 (April 1998): 922–928, https://erj.ersjournals.com/content/11/4/922.long.

4. Conclusions

Between this paper and the paper that preceded it (here called Part I),[227] 27 agents (15 biological and 12 chemical) were studied for potential long-term effects from acute exposure. The conclusions from this paper and Part I are summarized here. Part I addressed the long-term effects of 17 agents, and this paper (Part II) addresses the long-term effects of 10 agents. Part I focused on agents that had no or little information on long-term effects, while Part II focuses on agents that had substantial information on long-term effects. All but two agents (ricin and T-2 mycotoxin) had some information about long-term sequelae, and all but four agents (ricin, T-2, plague, and SEB) had some long-term effects associated with the illness or agent. Sequelae ranged from mild to severe and common to uncommon.

Mild sequelae, such as slight increases in fatigue or anxiety, may not affect an individual's ability to perform tasks, but severe sequelae, such as difficulty breathing or memory problems, could affect his or her ability. Some sequelae, such as personality changes, amnesia, or blindness, are so severe and persistent that they could not only affect the individual's task performance, but also his or her entire future quality of life and potentially even his or her caregiver's life. Some sequelae, such as relapse, may require additional medical resources that would need to be taken into account during planning. Therefore, full characterization of potential long-term effects (as best as possible from the literature available) is important for determining the overall effect of a chemical or biological agent or illness.

The long-term effects from biological agents were split into five categories: no effect, mild effect, relapse, severe effect, or not applicable (N/A). Sequelae may be overrepresented in the literature for some agents since those who do not have long-term effects often do not follow up with a doctor. Three agents produced "no effect" in the long-term: treated plague, treated tularemia, and SEB. "Mild effect" was defined as an effect that would not have a significant effect on the person's life or an effect that lasted less than 1 year and was not debilitating (e.g., chronic fatigue). The five agents that produced mild effects were Q fever (chronic fatigue syndrome), VEE and WEE (slight hand tremor or insomnia), untreated tularemia (acute symptoms that could last 15 months), and untreated brucellosis (acute symptoms that could last years). "Relapse" was defined as an illness with periods of remission and reappearance of the same symptoms, often with the same severity, either in untreated or treated cases (even with proper antibiotic use). Untreated and treated

[227] Bishop and Curling, *Analysis of Non-Acute, Sub-Lethal Chemical/Biological Injuries and Illnesses*.

brucellosis, glanders, and melioidosis all had moderate (3%–50%) rates of relapse, with symptoms similar to or less severe than those of the original illness. "Severe effect" was defined as an illness with long-term effects that last more than a year and that would have a significant effect on the quality of life or health resources (beyond antibiotics). Six agents produced severe effects at least some of the time: smallpox (produces blindness <1% of the time), Q fever (produces endocarditis or other localized infections <1% of the time), brucellosis (produces endocarditis, neurobrucellosis, or other localized infections <3% of the time), EEE (produces moderate rates of long-term neurological sequelae when it manifests as encephalitis), anthrax (produces significant respiratory difficulties in >50% of people), and botulism (produces weakness, exercise intolerance, and difficulty breathing/speaking/swallowing in >50% of people). "N/A" was defined as illnesses for which no data were available on chronic effect (ricin, T-2) or illnesses with ~100% lethality (untreated anthrax and plague). Some categories are subjective. The biological agents are categorized in Table 8.

Long-term effects of chemical agents were categorized by the body system affected (neurological, respiratory, ocular, and/or skin). Almost all reports of exposure to chemical agents were treated, so no conclusions on long-term effects from untreated exposures could be given. Most agent effects were localized to one or two body systems, and the most commonly affected systems were neurological and respiratory. Some agents produced sequelae only after severe or very severe acute exposures, while others also produced sequelae after mild or moderate acute exposures. Because most reports did not include the exact agent dose, doses are inferred from acute symptoms.

Nerve agents (tabun, sarin, soman, cyclosarin, and VX), hydrogen cyanide, cyanogen chloride, and hydrogen sulfide can produce neurological sequelae, but most severe sequelae only occur in those who had doses that were high enough to produce severe or very severe acute symptoms. Neurological sequelae can include sleep disorders, irritability, memory problems, personality changes, or coma. Most of the agents that affect the neurological system can produce brain damage at very high doses, which leads to the severe symptoms and often massive declines in the quality of life. The brain damage from nerve agents typically comes from seizures, while the brain damage from hydrogen sulfide, hydrogen cyanide, or cyanogen chloride typically comes from anoxia. Nerve agents and hydrogen sulfide have been reported to produce more mild symptoms at lower acute doses.

Sulfur mustard, phosgene, chlorine, and ammonia can produce respiratory sequelae. Respiratory sequelae can include chronic bronchitis, difficulty breathing, or cough. Respiratory sequelae are often tied to dose (the exception being phosgene), but long-term respiratory effects following mild or moderate acute exposure are much more common than effects in other bodily systems. Phosgene, chlorine, and ammonia are all irritant gases and therefore produce similar respiratory effects. Ocular sequelae, including corneal scratches, decreases in vision, or blindness, can occur after sulfur mustard injury or splashes of

ammonia in the eye. Ocular sequelae are generally the rarest. Skin sequelae include scarring, hyper-/hypo-pigmentation, skin lesions, itching, or dry skin and can occur after sulfur mustard injury. The chemical agents are categorized in Table 9.

All agents were categorized in Part I using similar categories to those shown here, although a full analysis of the literature had not yet been performed for 10 of the agents. Most agents did not change categorized effects between the analyses in Part I and Part II. The categorization of agents in Table 8 and Table 9 is broad and therefore does not pick up some of the more subtle changes described earlier in the document upon completion of the full literature review for the 10 agents. Part II provides a better description of the relapse rate from melioidosis, the localized infections from brucellosis and Q fever, the duration of untreated brucellosis, the long-term effects of tabun, soman, cyclosarin, and VX, the rates of lung complications from sulfur mustard and chlorine, and the rates of skin and ocular complications and cancer risk from HD. Thus, the fuller literature review in Part II provides a better understanding of the long-term effects of the 10 agents, especially agents that can produce many different kinds of long-term effects (e.g., brucellosis or sulfur mustard) or that produce effects that are often overestimated in reviews (e.g., melioidosis or chlorine). When combined, the descriptions of long-term effects from chemical and biological agents in Part I and Part II of this series provide a good basis for understanding not only the acute effects of chemical and biological illnesses or injuries, but also what to expect in the months and years to come after the initial exposure.

Table 8. Effects of Biological Agents

Not Applicable	No Effect	Mild Effect	Relapse	Severe Effect
Anthrax (Un) – 100% fatality rate	Plague (Tr) – no effects found upon follow-up	Q fever (Un and Tr) – Chronic Fatigue Syndrome (CFS) in ~20% for years afterwards	Brucellosis (Un) – can produce relapsing illness for years	EEE (Un) – can have mild to severe neurological sequelae, secondary to encephalitis (33%)
Plague (Un) – 100% fatality rate	SEB (Un) – no effects found upon follow-up	VEE (Un) – rarely, can have slight hand tremor or weakness	Brucellosis (Tr) – relapse in 5%–15% of those treated with full antibiotic regimen	Botulism (Un and Tr) – after moderate or severe acute symptoms, can have weakness, difficulty speaking/ swallowing, and so forth. (~50%)
Ricin – no information	Tularemia (Tr) – no effects found upon follow-up	WEE (Un) – rarely, can have slight hand tremor or weakness	Glanders (Un and Tr) – relapse days to years after	Q fever (Un and Tr) – endocarditis/vascular infection (1%), almost always in those with previous valve/heart conditions
T-2 – no information		Tularemia (Un) – can last up to 15 months	Melioidosis (Un) – same as glanders	Brucellosis (Un and Tr) – localized infections (1%–7%) in heart or nervous system
		Brucellosis (Un) – can produce sustained illness for years	Melioidosis (Tr) – relapse in <5% of those treated with full antibiotic regimen	Smallpox (Un) – blindness in <1%
				Anthrax (Tr) – decreased lung function in >50%

Legend: Neurological | Acute Symptoms Last More than 3 Months | Relapse of Acute Symptoms | Localized Infection | Other

Note: EEE = Eastern Equine Encephalitis, SEB = Staphylococcal Enterotoxin B, VEE = Venezuelan Equine Encephalitis, WEE = Western Equine Encephalitis, Un = untreated, Tr = treated.

Table 9. Effects of Treated Chemical Agents

Exposure	Neurological	Respiratory	Ocular	Skin
Mild/Moderate Acute Exposure	Sarin – most recover completely, some have anxiety, depression, or memory problems after Tabun, soman, cyclosarin, VX – same as sarin	Sulfur mustard – chronic bronchitis and other lung effects in ~30%–50%, worsens over time Phosgene – some have difficulty breathing up to 3 years afterwards Chlorine – RADS in a few for up to 6 months	Sulfur mustard – ocular injuries in <10%	Sulfur mustard – mild effects, including skin lesions, dry skin, itching, and burning in ~40%
	Hydrogen sulfide – headache, balance in ~30%			
Severe/Very Severe Acute Exposure	Sarin – after seizures can have brain damage Tabun, soman, cyclosarin, VX – same as sarin	Sulfur mustard – chronic bronchitis and other lung effects in ~30%–50%, worsens over time Ammonia – smokers especially have difficulty breathing up to 10 years afterwards Phosgene – some have difficulty breathing up to 3 years afterwards Chlorine – RADS in ~30% for up to 6 months	Sulfur mustard – ocular injuries and/or corneal scarring in ~10% Ammonia – blindness after spraying eyes	Sulfur mustard – mild effects, including skin lesions, dry skin, itching, and burning in ~40%
	Hydrogen sulfide – severe neurological sequelae from anoxic brain damage in ~30%–50% Hydrogen cyanide – ~40% neurological sequelae from anoxic brain damage Cyanogen chloride – same as hydrogen cyanide			

Legend: Severe Effects from Seizures | Severe Effects from Anoxia | Sulfur Mustard | Irritant Gases

Note: RADS = Reactive Airways Dysfunction Syndrome.

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Appendix A.
Illustrations

Tables

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Appendix B.
References

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Appendix C.
Abbreviations

AC	hydrogen cyanide
AMedP	Allied Medical Publication
CBRN	chemical, biological, radiological, and nuclear
CFS	Chronic Fatigue Syndrome
CG	phosgene
CK	cyanogen chloride
Cl_2	chlorine
COPD	Chronic Obstructive Pulmonary Disease
ECBC	Edgewood Chemical Biological Center
EEE	Eastern Equine Encephalitis
EEG	electroencephalogram
GA	tabun
GB	sarin
GD	soman
GF	cyclosarin
H_2S	hydrogen sulfide
HD	sulfur mustard
IDA	Institute for Defense Analyses
IED	improvised explosive device
IV	intravenous
LD_{50}	dose producing lethal effects in 50% of the population
MMWR	Morbidity and Mortality Weekly Report
N/A	Not Applicable
NATO	North Atlantic Treaty Organization
NH_3	ammonia
OP	organophosphate
PCR	polymerase chain reaction
PTSD	post-traumatic stress disorder
RADS	Reactive Airway Dysfunction Syndrome
REM	rapid eye movement
SEB	staphylococcal enterotoxin B
TMP-SMX	trimethoprim + sulfamethoxazole
Tr	treated
UK	United Kingdom
Un	Untreated
U.S.	United States of America
VEE	Venezuelan Equine Encephalitis
VX	O-Ethyl-S-(2-diisopropylaminoethyl) methyl phosphonothiolate
WEE	Western Equine Encephalitis

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REPORT DOCUMENTATION PAGE	Form Approved OMB No. 0704-0188

1. REPORT DATE (DD-MM-YYYY)	2. REPORT TYPE	3. DATES COVERED (From – To)
XX-01-2019	Final	

4. TITLE AND SUBTITLE	5a. CONTRACT NO.
Analysis of Non-Acute, Sub-Lethal Chemical/Biological Injuries and Illnesses, Part II	HQ0034-14-D-0001
	5b. GRANT NO.
	5c. PROGRAM ELEMENT NO(S).

6. AUTHOR(S)	5d. PROJECT NO.
Kristen A. Bishop	
	5e. TASK NO. CA-6-4445
	5f. WORK UNIT NO.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NO.
Institute for Defense Analyses Strategy, Forces and Resources Division 4850 Mark Center Drive Alexandria, VA 22311-1882	IDA Paper P-10390 Log: H 18-000529

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR'S / MONITOR'S ACRONYM(S)
Office of the Surgeon General DHHQ 7700 Arlington Blvd. Falls Church, VA 22042-5143	OTSG
	11. SPONSOR'S / MONITOR'S REPORT NO(S).

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution is unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This report is a continuation of IDA P-8865, which examined the long-term effects after acute exposures to the chemical and biological agents/agent classes described in Allied Medical Publication 7.5 (AMedP-7.5). In P-8865, ten agents were not fully described due to their large bodies of literature on long-term effects and the nature of the quick look study. This report describes the long-term effects of the ten agents: brucellosis, melioidosis, Q fever, sulfur mustard, chlorine, tabun, sarin, soman, cyclosarin, and VX.

15. SUBJECT TERMS

long-term, sequelae, chronic, biological warfare, chemical warfare, AMedP-7.5, symptoms, relapse, brucellosis, melioidosis, Q fever, nerve agents, tabun, sarin, soman, cyclosarin, VX, sulfur mustard, chlorine

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NO. OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			MAJ Thomas Rezentes Jr.
U	U	U	U	92	19b. TELEPHONE NUMBER (Include Area Code) (703) 681-8188

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