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

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Executive Summary

Since 1994, the Institute for Defense Analyses (IDA) has supported the U.S. Army Office of the Surgeon General (OTSG) in its planning, preparation, and exercises to defend against chemical, biological, radiological, and nuclear (CBRN) weapons use against U.S. military personnel. One of the major efforts for this task was producing the *NATO Allied Medical Publication 7.5 (AMedP-7.5) NATO Planning Guide for the Estimation of CBRN Casualties.*[1] *AMedP-7.5* provides information on the acute effects of 23 chemical or biological agents/agent classes and of radiation and nuclear weapons, but, by design, does not include the potential long-term effects that can result from CBRN injury. These effects are not relevant on a battlefield but could have significant effects on the military and veteran medical systems, on the casualties, and on the individuals' ability to serve on the force. This paper includes a quick look at the potential long-term effects of the 23 chemical and biological agents/agent classes described in *AMedP-7.5*. Long-term effects of radiological and nuclear injury have been extensively described in other sources and are not included in this paper.

"Long-term effects" in this paper were defined as effects that lasted for longer than 3 months after the acute injury (or appeared after 3 months), occurred after an acute injury rather than chronic exposure, and were the direct result of the agent rather than a countermeasure. In addition, agents and routes of exposure that were not covered in *AMedP-7.5* are not included in this paper, which, for biological agents, means that we only covered inhalational exposure. For chemical agents, we only covered inhalational exposure unless skin or eye effects were noted in *AMedP-7.5*.

The long-term effects of biological agents were separated by two metrics. One was the approximate frequency of the long-term effect. The categories for this were "<3%," "~3%–50%," and ">50%" of acute cases. These values are rough estimates since they are often based on small numbers of reports and follow-up after illness/injury is often not performed. In addition to frequency, the type of long-term effect was categorized as "no effect," "mild effect," "relapse," "severe effect," or "not applicable." Agents with "no effect" had no long-term effects described in the literature, and/or all who were followed up with after the acute illness had no sequelae. Agents with "mild effect" produced long-term effects that were not debilitating but did present after acute illness. Examples of mild

[1] 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).

effects include insomnia, chronic fatigue, and mild hand tremor. Agents that produced "relapse" produced the same or similar symptoms as the acute illness after a period of remission. Relapse can occur either in treated or untreated patients, including those who took the full course of antibiotics (relapse following improper antibiotic use was not included). Agents that produced "severe effects" produced effects that would be debilitating and could drastically affect not only the life of the patient, but potentially also his or her caregivers. Examples of severe effect include blindness, personality changes, difficulty breathing, and difficulty performing basic tasks, such as self-feeding. The agents categorized as "N/A" either did not have any follow-up described in the literature (e.g., ricin) or have a ~100% fatality rate (e.g., untreated inhalational anthrax). Table ES-1 shows the effects of biological agents.

Table ES-1. Effects of Biological Agents

Percent of Population with Long-Term Effect	No Effect	Mild Effect	Relapse	Severe Effect	N/A
<3% of cases				Smallpox	
				Q Fever (Un and Tr)	
~3%–50% of cases		Q Fever (Un and Tr)	Brucellosis (Un and Tr)	EEE	
		VEE	Glanders (Un and Tr)		
		WEE	Melioidosis (Un and Tr)		
		Tularemia (Un)			
>50% of cases	Plague (Tr)			Anthrax (Tr)	Anthrax (Un)
	SEB			Botulism (Un and Tr)	Plague (Un)
	Tularemia (Tr)				Ricin
					T-2

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

The effects of chemical agents were categorized differently. Long-term effects of chemical agents often are dependent on the initial dose (here categorized by severity of acute symptoms as a surrogate for initial dose since initial dose was rarely known) and are usually localized to specific organ systems. Therefore, chemical agents were categorized by dose-response ("no dose effect/none reported," "some dose effect," or "only in severe") and by organ system (neurological, respiratory, ocular, or dermatological). Agents with "no dose effect" showed no link between initial dose and severity of the long-term effect,

and the severity was tied more to another factor, such as smoking. Agents with "some dose effect" could produce long-term effects after any exposure causing symptoms, but the effects were more severe or more likely at higher doses. An example agent is sulfur mustard, which produces more frequent ocular or skin damage or respiratory effects at higher doses but can also produce effects at low doses. Agents that produce sequelae "only in severe" do not produce long-term effects after exposures causing mild or moderate acute symptoms but can produce debilitating effects following severe or very severe acute symptoms. An example agent is hydrogen cyanide, which can lead to severe neurological sequelae, such as coma, personality changes, or tremors after severe or very severe acute symptoms, but not after mild or moderate acute symptoms. Table ES-2 shows the effects of treated chemical agents.

Table ES-2. Effects of Treated Chemical Agents

Dose Effect	Neurological	Respiratory	Ocular	Dermatological
No Dose Effect/None Reported		CG		
Some Dose Effect	Nerve H_2S	HD Cl_2	HD	HD
Only in Severe	AC CK	NH_3	NH_3	

Note: AC = hydrogen cyanide, CG = phosgene, CK = cyanogen chloride, Cl_2 = chlorine, H_2S = hydrogen sulfide, HD = sulfur mustard, NH_3 = ammonia.

This paper describes the potential long-term effects from agents described in *AMedP-7.5*. Many holes exist in the literature on the rates and types of long-term effects, and those gaps are presented in the paper. Although almost all of the agents were fully characterized in this document, a follow-up analysis is recommended for the following six agents or agent classes:

- Brucellosis,
- Melioidosis,
- Q Fever,
- Nerve Agents,
- Sulfur Mustard, and
- Chlorine.

These agents/agent classes had a large amount of literature available on long-term effects and could not be described fully in this quick-look analysis.

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Contents

1. Introduction

A. Background on *Allied Medical Publication 7.5* (*AMedP-7.5*)

Since 1994, the Institute for Defense Analyses (IDA) has supported the U.S. Army Office of the Surgeon General (OTSG) in the Medical Chemical, Biological, Radiological, and Nuclear (CBRN) Defense Planning & Response Project. This support includes OTSG's effort to develop and maintain a North Atlantic Treaty Organization (NATO) standard for estimating casualties that would result from battlefield CBRN attacks against Allied forces. This methodology is anticipated to be promulgated as *NATO Allied Medical Publication 7.5 (AMedP-7.5) NATO Planning Guide for the Estimation of CBRN Casualties.*[1] The methodology only focuses on acute injuries since those injuries would be relevant to a battlefield casualty scenario. This approach left a hole, though, by not reporting on potential long-term effects of the agents. Although long-term effects would not affect the time at which someone initially becomes a casualty and would not impair his or her immediate battlefield readiness, these long-term effects would affect the military medical system or the Veterans Administration, especially if the effects are severe. Many of these severe long-term effects (coma, personality changes, blindness, and so forth) would negatively affect the individual's and, potentially, the caregiver's quality of life and could cost the medical system considerable amounts of money.

AMedP-7.5[2] includes models for 12[3] chemical agents, 15 biological agents, and radiation and nuclear effects. In this paper, all of the chemical and biological agents were studied to determine the potential long-term effects of each agent. Long-term radiological and nuclear effects have been studied extensively elsewhere,[4] so this paper does not address them.

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1 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).

2 Ibid.

3 In this paper, 5 of the 12 chemical agents are grouped together as "nerve agents," so there are 8 sections on chemical agents/agent categories in Chapter 3.

4 National Research Council, *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2* (Washington, DC: National Academies Press, 2006), https://doi.org/10.17226/11340.

B. Previous Descriptions of Long-Term Effects

Some papers have been published on the long-term effects of select agents, but many of them were written 20 or more years ago or have reduced scope. The most extensive paper is a 2016 publication titled "Assessment of Potential Long-Term Health Effects on Army Human Test Subjects of Relevant Biological and Chemical Agents, Drugs, Medications, and Substances."[5] It is a literature review of the potential long-term effects from the agents and diseases tested in the Army's volunteer chemical or biological research programs between 1954 and 1975. Included among these agents and diseases are 11 agents/agent classes/diseases also described in this paper: Q fever, encephalitides (Eastern Equine Encephalitis (EEE), Western Equine Encephalitis (WEE), and Venezuelan Equine Encephalitis (VEE)), botulism, nerve agents, sulfur mustard, phosgene, tularemia, Staphylococcal enterotoxin B (SEB), and hydrogen cyanide. One of the limitations of the 2016 paper is that the authors only looked at articles and reviews published between June 30, 2006, and December 1, 2015. They stated that this time period was chosen because more recent science could disprove earlier studies, especially modern population studies vs. earlier case reports. The IDA team disagrees with this approach, however, since it biased some results, especially for diseases and agents that are seldom encountered today (e.g., encephalitis and phosgene) and for which few or no population-level studies have been performed. For example, due to the date range restrictions in the 2016 paper, the authors only found one case report describing sequelae of hydrogen cyanide exposure, while the IDA team found 30 cases describing the follow-up of patients who had been exposed to hydrogen cyanide. Because of this difference in approach, the 2016 paper was perused to enable the evaluation of relevant cited sources. IDA also analyzed each of the 11 agents separately. The other 12 agents described in this IDA paper were not included in the 2016 paper.

In addition, some extensive reviews have been produced for specific agents, and these reviews are referenced where applicable in this paper. They include Pechura and Rall's 1993 study on the long-term effects of sulfur mustard[6] and the National Academies' 2010 study on sarin.[7] These reviews were studied carefully, and relevant references were extracted. In addition, particular emphasis was placed on papers published since the 1993

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[5] Ho-Chunk Technical Solutions, "Assessment of Potential Long-Term Health Effects on Army Human Test Subjects of Relevant Biological and Chemical Agents, Drugs, Medications and Substances," TR-16-109 (Winnebago, NE: Healthcare Division, February 29, 2016), http://www.dtic.mil/get-tr-doc/pdf?AD=AD1009505.

[6] 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.

[7] 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.

or 2010 studies. For Pechura and Rall's study,[8] that included most of the papers that followed up with exposed Iranian soldiers and civilians after the Iran-Iraq War.

C. Scope of This Paper

This paper describes only the long-term effects from acute exposures. It does not include effects from chronic, long-term exposures, which may occasionally be used to provide additional evidence for a condition observed after acute exposure but are not the focus of this analysis. In addition, the time period used to distinguish "long-term effects" or sequelae from acute effects was 3 months. All of the effects that resolved within 3 months were described as "acute," while those that resolved after more than 3 months were described as "long-term." The timing was somewhat arbitrary, but it lined up with some of the time frames given in *AMedP-7.5*,[9] and virtually all effects that lasted at least 3 months did not resolve for months or years (if ever) after that.

In *AMedP-7.5*,[10] infrequent effects, such as those from encephalitis, were not included. In this analysis, however, small or infrequent effects were included since they often require substantial resources over a long period of time. Effects such as coma, personality changes, memory loss, or blindness may seldom occur, but, when they do, they can significantly affect the patients' and their caregivers' quality of life. They can also require large amounts of money for health care, disability payments, and other costs.

Since this paper is a quick-look analysis, it focuses only on the diseases and routes of exposure described in *AMedP-7.5*. It excludes any effects found only in children since children would not be in the military population.[11] In addition, it does not include chronic effects from countermeasures. All countermeasures are assumed to be taken in accordance with prescriptions. Relapses following improper antibiotic use, for example, are not discussed. This paper only looks at the long-term effects of the agents or diseases rather than the long-term effects from specific acute symptoms independent of the cause. For example, the long-term brain damage from hydrogen cyanide is generally ascribed to the brain tissue's inability to metabolize oxygen during the acute exposure. This paper characterizes the long-term effects found after exposure to hydrogen cyanide or cyanide salt but does not consider the long-term brain damage from other causes of lack of oxygen to the brain (drowning, carbon monoxide, strangulation, and so forth).

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[8] Institute of Medicine, *Veterans at Risk*.

[9] Oxford, *NATO AMedP-7.5*.

[10] Ibid.

[11] Not all papers gave exact ages, so "adults" were considered to be the population above 10 years of age.

The psychological effects arising from a terrorist attack or an accident in general, rather than psychological effects directly resulting from the agent or disease's pathology, were also not included in this study. It is anticipated, for example, that civilians subjected to a chemical or biological attack, such as those affected in the Amerithrax attack or the Tokyo subway attack, would have high levels of distress unrelated to specific symptoms from anthrax or sarin.

D. Methods

The literature review performed for this analysis primarily looked at case studies, review articles, and epidemiology studies. The instances described in these reports can occur from accidental, intentional, or natural exposures. Long-term effects of biological agents typically come from natural exposures. Long-term effects of chemical agents or toxins typically come from accidental or intentional exposures since these agents/toxins are not generally found in large quantities in nature. Chemical agents, therefore, are often described in case reports or reports from large numbers of people exposed in a specific incident (such as the Iran-Iraq War). Biological agents are usually described in larger epidemiological studies that include many separate incidents (except in the case of anthrax).

This quick-look analysis categorized agents by the amount of data available in the literature on their long-term effects. For studies with "no data," we did not find any animal or human studies that followed up with individuals after the initial course of illness (generally less than 2 weeks). Therefore, no conclusions could be drawn on whether long-term effects would occur after exposure to the agents. For studies with "little data," some information was available in the literature (generally case reports or epidemiological studies), but the amount of information was limited and could be easily described fully in this quick-look analysis. For studies with "more data," many papers and sometimes reviews have been published on long-term effects from the agent. Since this paper is a quick-look analysis, we could not sift through all of the papers on the topic of long-term effects of agents. Further study is recommended to provide a more thorough analysis.

When a full analysis of the literature was performed (for those agents that had "no" or "little data"), no time period (i.e., 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 symptoms" or "*agent* sequelae." If specific sequelae were known to occur from the agent (endocarditis, relapse, and so forth), we also searched for that sequelae plus the agent name. Relevant references were taken from papers found in the initial searches. Papers that did not give information on long-term effects (or lack thereof) and papers on chemical agents that did not include acute symptoms were not included. Papers written in foreign languages were not reviewed.

Chapter 2 describes the long-term effects of the biological agents in *AMedP-7.5*,[12] and Chapter 3 describes the long-term effects of the chemical agents. For agents with "no" or "little data," a box with the conclusions on long-term effects is found at the end of that section. The full analysis has not yet been performed for those agents with "more data," so the conclusions are not finalized. At the end of Chapters 2 and 3, conclusions are provided on the type of long-term effects and the frequency observed. Chapter 4 provides a longer conclusion, including recommendations for further analysis of certain agents.

[12] Ibid.

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2. Long-Term Effects of Biological Agents

Information on the effects of biological agents are often found from natural outbreaks of the disease, which can provide a useful source of knowledge on long-term symptoms. Although many diseases are only followed during the acute phase of illness before the patient is either released from the hospital or finishes treatment, some are followed for longer periods. In addition, intentional exposures, such as with anthrax,[13] or public health concerns, such as outbreaks of botulism[14] or Q fever,[15] tend to be followed more closely for long periods. This chapter discusses potential long-term effects of each of the biological agents described in *AMedP-7.5*.[16] Since this paper is a quick-look analysis, only a small subset of the literature available is discussed for some of the agents. Other agents with little or no literature on long-term effects were described in the best detail possible and with all the literature that was discovered, noting any gaps. A categorization of these agents for severity of long-term symptoms and the amount of literature still available on these agents is provided at the end of this chapter and in Chapter 4.

A. Anthrax

Inhalational anthrax is caused by the bacterium *Bacillus anthracis* and, in the acute phase, produces malaise, fatigue, fever, respiratory distress, and eventual cardiovascular and neurological distress, often ending in death.[17] Since untreated inhalational anthrax has a mortality rate of almost 100%, it does not have any long-term effects. Treated anthrax

[13] Dori B. Reissman et al., "One-Year Health Assessment of Adult Survivors of *Bacillus anthracis* Infection," *Journal of the American Medical Association* 291, no. 16 (2004): 1994–1998, doi:10.1001/jama.291.16.1994.

[14] Centers for Disease Control and Prevention, "Botulism from Drinking Prison-Made Illicit Alcohol — Utah 2011," *Morbidity and Mortality Weekly Report* 61, no. 39 (October 5, 2012): 782–784, https://www.cdc.gov/mmwr/pdf/wk/mm6139.pdf.

[15] 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 (1 August 2002): 539–546, https://academic.oup.com/qjmed/article/95/8/539/1698443.

[16] Oxford, *NATO AMedP-7.5*.

[17] Ibid., 19-7.

has a mortality rate of 45%–70%[18] in the few human cases documented. The treatments include antibiotics and often extensive supportive care.

Only one paper[19] could be found that described the course of disease beyond initial hospitalization. Reissman et al.[20] followed up with 15 of the 16 survivors from the 2001 anthrax attacks a year after the incident, 8 of whom had not returned to work since (5 of the 6 inhalational patients and 3 of the 9 cutaneous patients). Of the 15 survivors, 6 had inhalational anthrax disease while 9 had cutaneous anthrax disease. Each of the six survivors who inhaled anthrax a year prior reported moderate to severe cardiopulmonary symptoms. Five of the six survivors reported moderate to severe head and neck, psychiatric, and/or orthopedic symptoms, and half reported moderate to severe muscular and/or neurological symptoms. Half of the survivors had clinically relevant distress, as measured with the Global Severity Index (GSI),[21] and four had been tested for and diagnosed with mild (three survivors) or severe (one survivor, could not actually complete the test) pulmonary dysfunction.[22]

Since Reissman et al. was the only paper that discussed chronic symptoms of treated anthrax exposure, further literature analysis is not recommended at this time. This recommendation may be revisited in a few years if interest in potential long-term effects of anthrax injury continues and new papers related to the topic are published. From this single paper, it should be assumed that those who are treated after developing symptoms of inhalational anthrax exposure would be unlikely to completely recover after the incident, at least within the first year, particularly with regards to pulmonary and psychological state. Of course, it is difficult to tell how much of the change in psychological state is due to the fact that they were attacked with a biological agent rather than the fact that this agent was anthrax.

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[18] Bret K. Purcell, Patricia L. Worsham, and Arthur M. Friedlander, "Anthrax," chap. 4 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), 75–76, https://ke.army.mil/bordeninstitute/published_volumes/biological_warfare/BW-ch04.pdf.

[19] Reissman et al., "One-Year Health Assessment of Adult Survivors."

[20] Ibid.

[21] Leonard R. Derogatis, *Symptom Checklist-90-R: Administration, Scoring, and Procedures Manual* (Minneapolis, MN: Pearson, 1994).

[22] Reissman et al., "One-Year Health Assessment of Adult Survivors."

Conclusions: Untreated inhalational anthrax is assumed to be 100% fatal. Treated inhalational anthrax leads to decreases in lung function and moderate to severe cardiopulmonary, muscular, and/or neurological symptoms (based on symptomatic survivors of the 2001 Amerithrax attack).

Caveats:

- **Only one paper addressed inhalational anthrax's long-term effects and included only six individuals.**
- **Cannot tell whether the psychological effects were from the anthrax itself or from the trauma associated with a terrorist attack.**
- **Only described chronic effects up to 1 year after illness.**

B. Brucellosis

Brucellosis is caused by bacteria in the genus *Brucella*. When untreated, brucellosis can be a prolonged illness. Bassett-Smith[23] and Simpson[24] stated that brucellosis symptoms can last up to 2 years or more. Brucellosis is often split into three types based on duration: acute (<8 weeks), sub-acute (8–52 weeks), and chronic (>52 weeks).[25] Acute symptoms include fever, sweats, chills, headache, malaise, fatigue, weight loss, arthralgia, and myalgia.[26] Approximately 5%–7% of infections have been characterized as "chronic".[27] The chronic form of the illness has an appearance that is similar to the acute form, although there may be remission and relapse during the illness, leading to brucellosis's original name of "undulant fever." In Simpson's[28] 90 patients, he observed that 11% of them had remissions that lasted between 1 week and several months before fever and associated symptoms returned. The other 89% only had one febrile episode. Bassett-Smith[29] similarly described a prolonged illness with some relapses. Those relapses were generally less severe than the

[23] 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/.

[24] 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.

[25] Marshall D. Fox and Arnold F. Kaufmann, "Brucellosis in the United States, 1965–1974," *The Journal of Infectious Diseases* 136 (August 1977): 312–316, https://www.jstor.org/stable/pdf/30081487.pdf.

[26] 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), 20-16–20-20.

[27] Fox and Kaufmann, "Brucellosis in the United States, 1965–1974"; M. R. Hasanjani Roushan et al., "Epidemiological Features and Clinical Manifestations in 469 Adult Patients with Brucellosis in Babol, Northern Iran," *Epidemiology & Infection* 132, no. 6 (December 2004): 1109–1114, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2870202/.

[28] Simpson, "Undulant Fever (Brucelliasis)."

[29] Bassett-Smith, "Mediterranean or Undulant Fever."

initial febrile episode. Some of the complications, however, such as spleen or liver involvement, can become more severe in later bouts of illness.[30] Liver and spleen involvement are the most common focal complications (i.e., symptoms at a particular site for at least 7 days) from brucellosis.[31] Fox and Kaufmann.[32] found that 27.7% of their brucellosis cases had some form of focal complication.

The most serious complication from brucellosis is endocarditis. However, it is a relatively rare complication, and only occurs in 1%–2% of patients.[33] It is the most common cause of death from brucellosis, and treatment generally requires prolonged antibiotics and surgery.[34] If the patient survives and is adequately treated, he or she can recover within 2 to 3 years.[35]

Relapses are common not only in untreated cases, but also in treated cases. Relapses can be minimized by completing the full course of antibiotics and using multiple antibiotics. The relapse rate is 8.4%, for example, from treatment with oral doxycycline plus rifampin, a common and effective treatment for brucellosis.[36] Patients who are given less effective treatments or who do not complete the full course of antibiotics have higher relapse rates.

The data for brucellosis primarily come from case reports that detail the illness profiles of several hundred cases at a time, such as those written by Simpson[37] and Fox and Kaufmann.[38] These reports often describe the entire course of illness, including any relapses or chronic conditions, such as endocarditis. Although a few papers have been described in this current IDA paper, we recommend a fuller analysis of the chronic effects of brucellosis. Analyzing the full body of literature could provide a better description of rate of incidence, duration, and severity of chronic symptoms of brucellosis.

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[30] Ibid.

[31] 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.

[32] Fox and Kaufmann, "Brucellosis in the United States, 1965–1974."

[33] 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; Roushan et al., "Epidemiological Features and Clinical Manifestations."

[34] Reguera et al., "*Brucella* Endocarditis."

[35] Wendell H. Hall, "Modern Chemotherapy for Brucellosis in Humans," *Reviews of Infectious Diseases* 12, no. 6 (November–December 1990): 1060–1099, http://www.jstor.org/stable/4455709.

[36] Ibid.

[37] Simpson, "Undulant Fever (Brucelliasis)."

[38] Fox and Kaufmann, "Brucellosis in the United States, 1965–1974."

C. Glanders

Glanders is a rare condition and has become even rarer since the decline in the use of horses for transportation.[39] It is caused by the bacteria *Burkholderia mallei*. Many of the natural cases result from direct contact with horses, so, in these cases, trying to determine whether glanders was contracted by aerosol or another method, such as through abraded skin, is usually impossible. Although glanders is often fatal, if someone develops glanders and survives, the illness can transition into a chronic form.[40]

Untreated glanders frequently becomes chronic, often with no change in symptomatology.[41] Some of the most common symptoms of acute glanders are abscesses, ulcerations, fever, chills, cough, nasal discharge, diarrhea, emaciation, dyspnea, and delirium.[42] Chronic glanders has periods of acute symptoms and then remission lasting weeks to years before relapse.[43] Lesions often form or reform, and the infection can become localized; however, as with acute glanders, symptoms can be highly variable between patients. Due to the sometimes long durations of remission before acute illness, it is difficult to determine when or if chronic glanders is completely cured.

Few studies have been performed on treated glanders because the disease is rare, particularly since the dawn of antibiotics. Seven cases of laboratory-acquired infection at Fort Detrick (Maryland) between 1945 and 1953 were documented.[44] All cases were successfully treated with 10 to 36 days of antibiotics, and the recovery time after treatment ranged from immediate to 188 days. Another case of laboratory-acquired infection occurred in 2000.[45] The patient was treated with a 10 day supply of clarithromycin a few weeks after the symptoms began but then relapsed 4 days later with respiratory distress and multiple hepatic and splenic abscesses. He later had a 6 month course of treatment and eventually

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[39] Bridget C. Gregory and David M. Waag, "Glanders," chap. 6 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), 125, https://ke.army.mil/bordeninstitute/published_volumes/biological_warfare/BW-ch06.pdf.

[40] Ibid., 128.

[41] George Dougall Robins, *A Study of Chronic Glanders in Man with Report of a Case, Analysis of 156 Cases Collected from the Literature, and an Appendix of the Incidence of Equine and Human Glanders in Canada*, Vol. 2, Issue 1, Studies from the Royal Victoria Hospital in Montreal, Québec (Montreal, Canada: Guertin Printing Company, 1906).

[42] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 21-6–21-8.

[43] J. F. Burgess, "Chronic Glanders," *Canadian Medical Association Journal* 34, no. 3 (March 1936): 258–262, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1561549/.

[44] Gregory and Waag, "Glanders."

[45] Arjun Srinivasan et al., "Glanders in a Military Research Microbiologist," *The New England Journal of Medicine* 345, no. 4 (July 26, 2001): 256–258. doi:10.1056/NEJM200107263450404.

recovered. The delay in antibiotic treatment may have increased his chances for relapse, so prompt antibiotic therapy would be especially important for glanders.[46]

Since glanders is such a rare disease, few cases of chronic glanders are available from which to glean information. Due to the dearth of papers on chronic glanders, further literature analysis is not recommended at this time. This recommendation may be revisited in a few years if interest in potential long-term effects of glanders injury continues and new papers related to the topic are published. Although glanders patients may relapse after prolonged periods of remission, insufficient data are available to quantify the expected rates or timing of relapse.

Conclusion: Glanders—treated and untreated—can lead to relapse. For untreated glanders, time between relapses can last days to years, and symptoms between the acute illness and relapses are similar.

Caveats:

- **Few descriptions of untreated or treated glanders are available, so the rate of recurrence could not be determined.**
- **The progression of illness for glanders can be highly variable, so the exact duration of chronic effect or remission of symptoms could not be determined.**

D. Melioidosis

Melioidosis is caused by the bacterium *Burkholderia pseudomallei*, which is closely related to the causative agent of glanders (*Burkholderia mallei*).[47] Due to this relationship, the symptoms of acute and chronic melioidosis are similar to those of glanders. Untreated melioidosis can go into remission and subsequently relapse, similar to untreated glanders. Abscesses and draining sinuses are common in relapsed melioidosis, and the chronic condition can last for years, including years-long gaps between relapses.[48]

Relapse after treatment is also a significant problem for melioidosis. In a study of 118 patients in northeast Thailand who had contracted melioidosis and were later followed long term, 27 relapsed (23%).[49] Three of those 27 patients relapsed twice. The median time between discharge from the hospital and subsequent relapse was 21 weeks. Chaowagul

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[46] Gregory and Waag, "Glanders."

[47] 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.

[48] 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.

[49] 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.

et al. found that those patients with a more severe acute disease, involving multiple foci of infection, were more likely to relapse than those with localized melioidosis. Of those patients who relapsed, 27% died.[50] A subsequent study of 116 patients at the same hospital with recurrent melioidosis found that 75% of the cases were caused by the same strain, while 25% of the cases were infection from a new strain (so not true relapse).[51] A short courses of antibiotics led to more frequent relapses than combination treatments or longer treatments.[52] In a hospital in northern Australia, Chaowagul et al.[53] observed a much lower rate of relapse: 30 patients of 465 (6%).

The data for melioidosis primarily come from case reports and epidemiology studies of hundreds of hospital cases, such as those reported by Chaowagul et al.[54] These papers generally chronicle the full course of illness and often include information about follow-ups or relapses. Although a few cases have been described in this current IDA paper, we recommend a more in-depth analysis of the chronic effects of melioidosis to compile a greater list of cases and provide a more detailed description of the symptoms and rates of chronic forms of melioidosis.

E. Plague

Plague is caused by the bacterium *Yersinia pestis.* Although most natural incidents of plague start with a bubonic form which can eventually transition to a septicemic or pneumonic form, the pneumonic form would be the most likely illness after an aerosol attack.[55] Untreated pneumonic plague is approximately 100% fatal after fever, cough, and bloody sputum,[56] so it does not have any chronic effects. Few cases of treated pneumonic plague were found, particularly ones in which the patient survived. One person with pneumonic plague was treated and released in Uganda in 2004.[57] She still had difficulty walking and was experiencing shortness of breath when she was released from the hospital after 10 days of treatment, but she reported having no lingering symptoms 3 weeks after release. Another

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[50] Ibid.

[51] Bina Maharjan et al., "Recurrent Melioidosis in Patients in Northeast Thailand is Frequently Due to Reinfection Rather than Relapse," *Journal of Clinical Microbiology* 43, no. 12 (December 2005): 6032–6034. doi:10.1128/JCM.43.12.6032-6034.2005.

[52] Chaowagul et al., "Relapse in Melioidosis."

[53] Bart J. Currie, Linda Ward, and Allen C. Chang, "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.

[54] Chaowagul et al., "Relapse in Melioidosis."

[55] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 23-1.

[56] Ibid.

[57] Elizabeth M. Begier et al., "Pneumonic Plague Cluster, Uganda, 2004," *Emerging Infectious Diseases* 12, no. 3 (March 2006): 460–467, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3291454/.

set of four patients in Colorado were successfully treated with antibiotics for primary pneumonic plague, and no long-term effects were recorded for any of these patients.[58] Therefore, treated pneumonic plague does not appear to lead to chronic effects, although this observation is only based on five people. Due to the dearth of papers on chronic plague symptoms, further literature analysis is not recommended at this time. This recommendation may be revisited in a few years if interest in potential long-term effects of plague injury continues. Currently, an outbreak of pneumonic plague is occurring in Madagascar, with reports of over 1,000 cases.[59] This large outbreak could produce follow-up studies on the survival and long-term outcomes from pneumonic plague exposure and provide more knowledge on pneumonic plague illness.

Conclusion: Untreated pneumonic plague is assumed to be 100% fatal. No long-term symptoms were observed for five people who were treated for pneumonic plague (four in Colorado and one in Uganda), suggesting that pneumonic plague may not lead to chronic symptoms. More information on potential long-term effects may be available in a few years since an outbreak of pneumonic plague is occurring in Madagascar at the time of this paper's writing.

Caveats:

- **Only two papers, describing five patients, were found that had any discussion of potential long-term symptoms.**
- **Neither paper described follow-up with patients more than 3 weeks after release.**

F. Q Fever

Q fever is caused by the bacterium *Coxiella burnetii* and generally constitutes a febrile illness that lasts 1–3 weeks without treatment.[60] *Coxiella burnetii* was one of the agents tested in the Project Whitecoat program at Fort Detrick (Maryland), which evaluated the effect of some pathogens on human subjects.[61] A survey of 358 individuals exposed to live agents, vaccines, or other countermeasures, along with 164 control subjects, found no significant differences between the two groups thirty years after the initial exposure. Not enough people participated for researchers to be able to test whether exposure to specific

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[58] Janine K. Runfola et al., "Outbreak of Human Pneumonic Plague with Dog-to-Human and Possible Human-to-Human Transmission — Colorado, June–July 2014," *Morbidity and Mortality Weekly Report* 64, no. 16 (May 1, 2015): 429–434, https://www.cdc.gov/mmwr/pdf/wk/mm6416.pdf.

[59] World Health Organization, "Emergencies Preparedness, Response: Plague – Madagascar," Disease Outbreak News, 27 November 2017, http://www.who.int/csr/don/27-november-2017-plague-madagascar/en/.

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

[61] Phillip R. Pittman et al., "An Assessment of Health Status among Medical Research Volunteers Who Served in the Project Whitecoat Program at Fort Detrick, Maryland," *Military Medicine* 170, no. 3 (March 2005): 183–187, http://militarymedicine.amsus.org/doi/pdf/10.7205/MILMED.170.3.183.

agents or vaccines led to lingering effects. No other studies of the military research volunteers over time have been found for those given biological agents, although, following a lawsuit, the Army is providing comprehensive medical care to these individuals.[62] Over time, more information on these volunteers may come out of this enhanced care, so the subject may need to be reinvestigated in a few years.

Although severe chronic Q fever symptoms are infrequent, they can cause significant incapacitation. The most commonly described chronic condition is endocarditis, which is rare. In a follow-up study of 147 cases of Q fever in Solihull, West Midlands, United Kingdom, three cases (2%) had cardiomyopathy in the 10 years after their illness.[63] Palmer and Young[64] reported a much higher incidence of endocarditis (11%), but they were surveying primarily inpatients at hospitals and therefore may have omitted the milder cases of Q fever treated at home or on an outpatient basis, biasing the results. Q fever is often treated on an outpatient basis or is unreported and only rarely is it severe enough to require hospitalization.[65] In a study of 1,569 patients with Q fever in France and other countries, 12 (0.7%) had endocarditis.[66] Fenollar et al.[67] studied 102 patients other with Q fever endocarditis. Of those 102 patients, almost all (93%) had previous valvulopathies. Endocarditis can appear years after infection[68] and can last years, with a mortality rate of 31 to 65%.[69] Therefore, endocarditis can be severe but occurs infrequently and often in those with previous valvular damage or defects. Individuals with those defects may therefore need to be monitored closely for chronic effects.

Some have also suggested that Q fever can cause a chronic fatigue syndrome. Ayres et al.[70] found that 8.2% of patients with Q fever subsequently had chronic fatigue syndrome that was not associated with other co-morbidities. They did not find significant cardiac

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[62] 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/.

[63] Ayres et al., "Long-term Follow-up of Patients from the 1989 Q Fever Outbreak."

[64] 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.

[65] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 24-7.

[66] Florence Fenollar et al., "Risks Factors and Prevention of Q Fever Endocarditis," *Clinical Infectious Diseases* 33, no. 3 (1 Auguat 2001): 312–316, https://doi.org/10.1086/321889.

[67] Ibid.

[68] Palmer and Young, "Q-Fever Endocarditis in England and Wales, 1975–81."

[69] 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.

[70] Ayres et al., "Long-term Follow-up of Patients from the 1989 Q Fever Outbreak."

defects in those with chronic fatigue compared to others. Limonard et al.[71] found that 28 of 54 patients (52%) with Q fever in the Netherlands reported severe fatigue 1 year after infection. However, significant controversy has arisen over the existence of chronic fatigue syndrome following Q fever and whether it is psychosomatic.[72] People who had Q fever 2 years previously reported significantly higher rates of fatigue than controls (54.8% vs. 20%) but also had significantly higher scores for psychosocial complaints and hypochondria, suggesting that psychological factors may have contributed to the fatigue.[73] Another study found that cognitive behavioral therapy was effective at reducing fatigue in those with Q fever fatigue syndrome while long-term antibiotic therapy was not.[74] Some other much less common chronic Q fever manifestations include infection of vascular aneurysm or prosthesis, osteomyelitis, lung infections, and hepatitis.[75]

The studies described in this current IDA paper encompass a few of those found in the literature about chronic effects of Q fever, primarily endocarditis and chronic fatigue. The chances of chronic symptoms of Q fever, with or without treatment, however, are low, except for chronic fatigue. Since chronic fatigue is not very well characterized and may be related to psychological factors, trying to determine the severity of this symptom is difficult. This analysis included only a subset of the information available on chronic effects of Q fever. IDA recommends further analysis for a better understanding of the rate, severity, and duration of symptoms for endocarditis and chronic fatigue following Q fever.

G. Tularemia

Tularemia is a febrile illness caused by the bacterium *Francisella tularensis*.[76] From case studies before the antibiotic era, tularemia lasts approximately 1 to 15 months.[77]

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[71] G. J. M. Limonard et al., "Detailed Analysis of Health Status of Q Fever Patients 1 Year after the First Dutch Outbreak: A Case-Control Study," *Quarterly Journal of Medicine* 103, no. 12 (1 December 2010): 953–958, https://doi.org/10.1093/qjmed/hcq144.

[72] Ibid.

[73] 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.

[74] 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.

[75] Didier Raoult, "Treatment of Q Fever," *Antimicrobial Agents and Chemotherapy* 37, no. 9 (September 1993): 1733–1736, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC188061/.

[76] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 25-1.

[77] Martin E. Evans et al., "Tularemia: A 30-Year Experience with 88 Cases," *Medicine* 64, no. 4 (July 1985): 251–269, http://journals.lww.com/md-journal/Citation/1985/07000/Tularemia__A_30_Year_Experience_With_88_Cases.6.aspx.

Foshay[78] states that in his experience with untreated tularemia patients, the illness can last between 1 week and 15 months, with an average of 4 months. Convalescence was slow, with a gradual return to work over those 4 months. He did not differentiate between pneumonic tularemia and other forms, although he did state that the prognosis was worse if pneumonia was present.[79] In 9 of 44 laboratory-acquired cases, weakness, lassitude, and weight loss lasted for over 5 months and for 3 to 6 months in other patients.[80] Relapse is generally uncommon, and there appear to be few chronic effects after the initial presentation of disease. Little to no data are available on effects of untreated tularemia that lasts longer than 15 months.

When tularemia is treated with antibiotics, no chronic effects are apparent. A retrospective study on 88 patients with treated tularemia found that relapse was rare, and, unlike untreated tularemia, the course of illness was short: a week or less following treatment.[81] Another study of 42 patients with laboratory-acquired tularemia infections found that after antibiotics, fever subsided in almost all patients within 3 days and symptoms ceased within a week.[82] Five patients relapsed after finishing antibiotics (7–14 day regimen) with a much milder version of the disease than before. The disease quickly subsided after antibiotic treatment was started again.[83] This example indicates that treated tularemia has little to no long-term symptoms of, especially when a longer antibiotic regimen is given. As stated in Section 2.F, no effects of agent exposure were noticeable 30 years after Project Whitecoat volunteers had been exposed to tularemia (although tularemia could not be separated out from the other agents in the analysis).[84] Since few papers that described any (or lack thereof) chronic effects of untreated or treated tularemia were available, further literature analysis is not recommended at this time. This recommendation may be revisited in a few years if interest in potential long-term effects of tularemia injury continues and new papers related to the topic are published.

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[78] Lee Foshay, "Tularemia: A Summary of Certain Aspects of the Disease Including Methods for Early Diagnosis and the Results of Serum Treatment in 600 Patients," *Medicine* 19, no. 1 (February 1940): 1–84, http://journals.lww.com/md-journal/citation/1940/02000/tularemia__a_summary_of_certain_aspects_of_the.1.aspx.

[79] Ibid.

[80] Evans et al., "Tularemia: A 30-Year Experience with 88 Cases."

[81] Ibid.

[82] Edwin L. Overholt et al., "An Analysis of Forty-Two Cases of Laboratory-Acquired Tularemia: Treatment with Broad Spectrum Antibiotics," *American Journal of Medicine* 30, no. 5 (May 1961): 785–806, https://doi.org/10.1016/0002-9343(61)90214-5.

[83] Ibid.

[84] Pittman et al., "An Assessment of Health Status among Medical Research Volunteers."

Conclusion: Untreated tularemia can produce symptoms for up to 15 months. Relapse is uncommon, and almost no chronic effects are apparent after the acute disease has subsided. After treatment, tularemia symptoms generally subside in 1 week or less. Relapse is uncommon, and no long-term effects of treated tularemia have been discovered.

Caveats:

- **Most information is based on a few case reports, especially for untreated tularemia.**
- **Many discussions of symptoms of treated tularemia only follow the patient until any acute symptoms have subsided, rather than checking for long-term effects (although none have been described).**

H. Smallpox

Smallpox is an illness characterized by rash and fever and caused by the virus *Variola major*.[85] Smallpox was officially eradicated worldwide in 1980, and few case reports before that time described long-term effects. Fenner et al.[86] described a few rare complications, such as blindness in 0.54%–0.9% of survivors, residual corneal opacities in 2.1%–4.4%, and arthritis in 1.7% of survivors. These symptoms, however, are generally ill characterized and occur infrequently. No other documents found a description of the chronic effects of smallpox. Because the disease has been eradicated and no more documents could be found describing chronic effects, a further literature review is not recommended.

Conclusion: Smallpox has rarely been associated with severe chronic effects. Rare complications have included blindness in 0.54%–0.9% of survivors and residual corneal opacities in 2.1%–4.4% of survivors.

Caveats:

- **Only one paper (Fenner et al.[87]) describes chronic effects of smallpox; otherwise, only acute effects are described.**
- **Chronic effects of smallpox are rare (<4.4%) and ill characterized.**
- **Since smallpox has been eradicated, it is unlikely that new information about potential sequelae will be published in the future.**

[85] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 26-1.

[86] F. Fenner et al., *Smallpox and Its Eradication* (Geneva, Switzerland: World Health Organization, 1998), 47–50, http://www.who.int/iris/handle/10665/39485.

[87] Ibid.

I. Encephalitides (VEE, EEE, and WEE)

Three forms of encephalitis are described in *AMedP-7.5*: VEE, EEE, and WEE.[88] All three forms are caused by alphaviruses and have similar symptom profiles. Most symptomatic individuals experience a mild febrile illness.[89] Since the chronic effects for each agent are similar (if differing in severity), all three are discussed in this section.

AMedP-7.5[90] does not take into account the encephalitis syndrome for its injury profiles for VEE, EEE, and WEE due to the syndrome's low incidence in adults. As described in the introduction, in an analysis of long-term effects, however, low incidence effects may still be relevant since many of these effects require significant resources for many years or may necessitate monitoring individuals for effects that manifest later. Therefore, encephalitis and its chronic effects are discussed in this chapter, rather than merely the acute febrile syndromes described in *AMedP-7.5*.

EEE is the most severe of the three encephalitides and leads to the most lasting effects. Few cases of EEE occur each year, but several studies describe the symptoms from small outbreaks. Children are more likely to have severe disability following illness than adults, but disability is common in both.[91] For this paper, the child cases were excluded since they would not be members of a military population. There were 27 adult cases (>10 years of age)[92] described in the literature reviewed for this paper. Table 1 lists the sequelae information obtained from each case report.

Table 1. Outcomes of Adult Cases of EEE

Patient #	Patient Age	Outcome	Severity of Sequelae	Source
1	40–59	Moderate mental retardation and poor emotional state	Severe	Feemster (1957)[93]
2	40–59	No sequelae	–	Feemster (1957)
3	40–59	No sequelae	–	Feemster (1957)
4	40–59	No sequelae	–	Feemster (1957)

[88] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 27-1–27-2.

[89] Ibid., 27-1.

[90] Ibid.

[91] M. M. Przelomski et al., "Eastern Equine Encephalitis in Massachusetts: A Report of 16 Cases, 1970–1984," *Neurology* 38, no. 5 (May 1, 1988): 736–739, https://www.ncbi.nlm.nih.gov/pubmed/3362371.

[92] Not all sources provided exact ages for patients. For example, Przelomski et al. listed five individuals in the age range "10–49 years." Therefore, for this analysis, "adults" were considered to be above 10 years of age, although this consideration may skew the results.

[93] Roy F. Feemster, "Equine Encephalitis in Massachusetts," *The New England Journal of Medicine* 257, no. 15 (October 10, 1957): 701–704, http://www.nejm.org/doi/full/10.1056/NEJM195710102571504.

Patient #	Patient Age	Outcome	Severity of Sequelae	Source
5	15	1.5 months later: tremor and weakness of limbs after moderate exercise only complaint	Mild	Hart, Keen, and Belle (1964)[94]
6	16	No sequelae	–	Bigler et al. (1976)[95]
7	72	No sequelae	–	Bigler et al. (1976)
8	56	No sequelae	–	Bigler et al. (1976)
9	38	Sequelae (no further description)	N/A	Bigler et al. (1976)
10	39	No sequelae	–	Bigler et al. (1976)
11	14	No sequelae	–	Bigler et al. (1976)
12	45	No sequelae	–	Bigler et al. (1976)
13	10–49	No sequelae	–	Przelomski et al. (1988)[96]
14	10–49	No sequelae	–	Przelomski et al. (1988)
15	10–49	No sequelae	–	Przelomski et al. (1988)
16	10–49	Mild sequelae, emotional instability	Mild	Przelomski et al. (1988)
17	10–49	Severe sequelae, such as mental retardation, vegetative state, generalized seizures, or spastic quadriparesis	Severe	Przelomski et al. (1988)
18	50–69	No sequelae	–	Przelomski et al. (1988)
19	50–69	No sequelae	–	Przelomski et al. (1988)
20	43	Slow mentation (no mental history available)	Severe	Letson et al. (1993)[97]
21	36	No sequelae	–	Letson et al. (1993)
22	62	Hemiparesis (improved with rehabilitation)	Severe	Letson et al. (1993)

[94] Kenneth L. Hart, David Keen, and Edward A. Belle, "An Outbreak of Eastern Equine Encephalomyelitis in Jamaica, West Indies," *The American Journal of Tropical Medicine and Hygiene* 13, no. 2 (March 1964): 331–334, https://doi.org/10.4269/ajtmh.1964.13.331.

[95] W. J. Bigler et al., "Endemic Eastern Equine Encephalomyelitis in Florida: A Twenty-Year Analysis, 1955–1974," *The American Journal of Tropical Medicine and Hygiene* 25, no. 6 (November 1976): 884–890, https://doi.org/10.4269/ajtmh.1976.25.884.

[96] Przelomski et al., "Eastern Equine Encephalitis in Massachusetts."

[97] G. William Letson et al., "Eastern Equine Encephalitis (EEE): A Description of the 1989 Outbreak, Recent Epidemiologic Trends, and the Association of Rainfall with EEE Occurrence," *The American Journal of Tropical Medicine and Hygiene* 49, no. 6 (December 1993): 677–685, https://doi.org/10.4269/ajtmh.1993.49.677.

Patient #	Patient Age	Outcome	Severity of Sequelae	Source
23	10	No sequelae	–	Carrera et al. (2013)[98]
24	14.7	Recovered speech, comprehension, and ability to self-feed 18 months after discharge	Severe	Silverman et al. (2013)[99]
25	11.2	No sequelae	–	Silverman (et al. 2013)
26	11.5	No sequelae	–	Silverman et al. (2013)
27	13.3	Mild to moderate disability	Mild	Silverman et al. (2013)

Out of these 27 cases of EEE listed in Table 1, 9 cases (33.3%) had long-term complications. Although some were mild, such as tremor after moderate exercise or emotional instability, some were quite serious, such as moderate mental handicap or hemiparesis.

VEE and WEE are much less likely to cause severe complications in adults than EEE. Two young men (27 and 35 years of age) who contracted VEE from inhaling infected mouse droppings in a lab had a residual slight tremor in their hands and insomnia following recovery, although those effects gradually disappeared over several months.[100] A study of 74 people over the age of 10 in Texas who contracted VEE found that 10 of them had sequelae a month after illness.[101] The recurrent symptoms included headache, weakness, muscle pain, fatigue, and double vision. One 37-year-old man had decreased sensory function (taste, smell, and hearing) and mental slowness 1 month after illness. At 9 months to 1 year after illness, three people had complete resolution of symptoms, and five only had fatigability. The last two people had a reduced sense of taste or poor concentration in addition to fatigability.[102] Most other reports on large outbreaks of VEE described long-

[98] Jean-Paul Carrera et al., "Eastern Equine Encephalitis in Latin America," *The New England Journal of Medicine* 369, no. 8 (August 22, 2013): 732–744, doi:10.1056/NEJMoa1212628.

[99] Michael A. Silverman et al., "Eastern Equine Encephalitis in Children, Massachusetts and New Hampshire, USA, 1970–2010," *Emerging Infectious Diseases* 19, no. 2 (February 2013): 194–202, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3559032/.

[100] Edwin H. Lennette and Hilary Koprowski, "Human Infection with Venezuelan Equine Encephalomyelitis Virus – A Report on Eight Cases of Infection Acquired in the Laboratory," *Journal of the American Medical Association* 123, no. 17 (1943): 1088–1095, doi:10.1001/jama.1943.02840520004002.

[101] G. S. Bowen et al., "Clinical Aspects of Human Venezuelan Equine Encephalitis in Texas," *Bulletin of the Pan American Health Organization* 10, no. 1 (1976): 46–57, https://www.ncbi.nlm.nih.gov/pubmed/949558.

[102] Ibid.

term effects only in children (<15 years old), rather than adults.[103,] In addition to the 64 people with no sequelae described by Bowen et al.,[104] 11 other cases were found in which people were followed up with after VEE illness and had no sequelae.

Few cases were found describing any long-term effects of WEE. Most descriptions of large outbreaks did not include any information on sequelae. Waters[105] stated that of the 10 adults who contracted WEE in Manitoba, 8 had no sequelae. A 62-year-old man had persistent weakness in his arm, and a 38-year-old woman had personality changes and a loss of intellect following her illness. Two other studies described people who recovered fully from WEE, and one of these studies noted a man who had a slight tremor in his hands and eyelids for 1 year after illness, but the tremor disappeared 14 months after illness.[106] No other long-term effects of VEE or WEE were found from case studies, aside from those observed in children, which would not be relevant to a military population.

Like EEE, VEE and WEE are rare illnesses. Although a few case reports may be available that were not analyzed in this quick-look analysis, the conclusions from the case reports found remained the same, and further analysis of the long-term effects of WEE, EEE, and VEE is not recommended. The chances of chronic effects appear much lower for VEE and WEE than for EEE.

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[103] N. Joel Ehrenkranz and Arnoldo K. Ventura, "Venezuelan Equine Encephalitis Virus Infection in Man," *Annual Review of Medicine* 25 (1974): 9–14, https://doi.org/10.1146/annurev.me.25.020174.000301; Scott C. Weaver et al., "Venezuelan Equine Encephalitis," *Annual Review of Entomology* 49 (2004): 141–174, https://doi.org/10.1146/annurev.ento.49.061802.123422.

[104] Bowen et al., "Clinical Aspects of Human Venezuelan Equine Encephalitis in Texas."

[105] J. R. Waters, "An Epidemic of Western Equine Encephalomyelitis in Humans-Manitoba, 1975," supplement 1, *Canadian Journal of Public Health* 67 (May–June 1976): S28–S32.

[106] Herman Gold and Bettylee Hampil, "Equine Encephalomyelitis in a Laboratory Technician with Recovery," *Annals of Internal Medicine* 16, no. 3 (1 March 1942): 556–569, doi:10.7326/0003-4819-16-3-556.

Conclusion: Although encephalitis is rare (1.8% according to *AMedP-7.5*) for VEE, EEE, and WEE, it can cause significant long-term neurological defects. Only mild sequelae, including slight hand tremor or insomnia, were observed in adults with VEE. Two people had mild effects, and one had severe sequelae after WEE, but few descriptions of sequelae were found. For all encephalitides, the encephalitis syndrome was much more common for children and infants than for adults. EEE is the most severe of the three encephalitides, and 9 of 27 historical cases of EEE (33.3%) had long-term complications. At least six of these complications were severe, including inability to speak or self-feed or intellectual disability. Therefore, 22%–30% of adults with symptoms of EEE are anticipated to have severe neurological complications from the disease, although many of those who contract EEE are asymptomatic.

Caveats:

- **Most papers on WEE and VEE do not include information about long-term symptoms.**
- **Not all papers gave exact ages, so "adults" were considered to be above 10 years of age, although this may skew the results.**
- **There is likely bias in the data for EEE since those people with more severe symptoms are more likely to be described extensively than those with mild symptoms.**
- **Unlike in *AMedP-7.5*,[107] individuals with encephalitis symptoms are included since they can have significant long-term symptoms.**

J. Botulism

Botulism is caused by the botulinum toxin, a neurotoxin produced by the bacterium *Clostridium botulinum*.[108] Most of the botulism outbreaks reported in the literature are from foodborne outbreaks, while the primary concern for the military would be from inhalation. The symptom profiles for the two modes of entry, however, are similar,[109] so information from foodborne outbreaks were used to determine the chronic effects of botulism. There are seven major serotypes of the botulinum toxin, with type A producing the most severe symptoms. The model for *AMedP-7.5* is based on type A.[110] However, to incorporate as much data as possible, this section includes information on other serotypes.

Some reports of milder cases of botulism indicate that there were no sequelae. A report on 108 cases of botulism serotype B in France, for instance, reported no sequelae but also stated that only two of these patients required intensive care.[111] More severe cases,

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

[108] Ibid., 30-1.

[109] E. Holzer, "Botulism Caused by Inhalation," *Medizinische Klinik* 41 (October 1962) 1735–1738 (referenced in Zygmunt F. Dembek, Leonard A. Smith, and Janice M. Rusnak, "Botulism: Cause, Effects, Diagnosis, Clinical and Laboratory Identification, and Treatment Modalities," *Disaster Medicine and Public Health Preparedness* 1, no. 2 (November 2007): 122–134, https://doi.org/10.1097/DMP.0b013e318158c5fd).

[110] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 30-1.

[111] P. Roblot et al., "Retrospective Study of 108 Cases of Botulism in Poitiers, France," *Journal of Medical Microbiology* 40, no. 6 (June 1994): 379–384, doi:10.1099/00222615-40-6-379.

however, can lead to effects that last years. After eight prisoners contracted botulism type A from ingesting homemade alcohol, most of them still had symptoms 11 months after the illness.[112] The most common symptoms were weakness, loss of muscle mass, difficulty swallowing, and reflux. These prisoners were hospitalized for 2 to 58 days after their initial symptoms.

Two major studies looked at larger numbers of people with a history of botulism years after their initial illness. Mann et al.[113] interviewed 27 individuals who had foodborne type A botulism 9 or 10 months after the outbreak and sent them a written questionnaire 2 years after the outbreak. People who had contracted severe botulism (required mechanical respiratory assistance) had significantly more lingering symptoms at 9, 13, and/or 24 months than those who had contracted moderate botulism (clinically apparent ocular and/or bulbar involvement but no required mechanical respiratory assistance). They inquired about 11 symptoms related to botulism. Those individuals who had severe botulism reported an average of 6.2 symptoms at 9 or 13 months and 4.9 symptoms at 24 months. Some of the most frequent symptoms reported by this cohort were exercise intolerance, general weakness, dry mouth, shortness of breath, difficulty speaking, and shoulder/arm weakness. Those individuals who had moderate botulism reported an average of 2.4 symptoms at 9 or 13 months and 1.7 symptoms at 24 months. The most frequent symptoms reported by this cohort were exercise intolerance, general weakness, dry mouth, and shortness of breath. Since these symptoms were self-reported, they may be biased if compared to doctor notes; however, they do give an indication of the length of time required to recover from botulism.

Gottlieb et al.[114] studied 211 people in the Republic of Georgia who had botulism at least 6 months before the study (average was 4.3 years). In the study, only 34 cases were laboratory confirmed: 33 were type B and 1 was type E. Most botulism cases in Georgia are type B, so Gottlieb et al. assumed that most of the remaining cases were also type B. The average age of patients was 37, and they were compared against age-, income-, and location-matched controls. Those patients who had contracted botulism were significantly more likely to report fatigue (50% vs. 28%), weakness (45% vs. 25%), dizziness, difficulty moving heavy objects and performing vigorous activities, and dry mouth.[115] Those patients who had contracted botulism also scored worse on a test for psychosocial well-being, especially "feeling full of pep" (20% vs. 55%). These symptoms were also self-reported,

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[112] Centers for Disease Control and Prevention, "Botulism from Drinking Prison-Made Illicit Alcohol."

[113] Jonathan M. Mann et al., "Patient Recovery from Type A Botulism: Morbidity Assessment Following a Large Outbreak," *American Journal of Public Health* 71, no. 3 (March 1981): 266–269, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1619789/.

[114] Sami L. Gottlieb et al., "Long-Term Outcomes of 217 Botulism Cases in the Republic of Georgia," *Clinical* Infectious *Diseases* 45, no. 2 (15 July 2007): 174–180, https://doi.org/10.1086/518890.

[115] Ibid., 174.

as in Mann et al.,[116] and there was no objective assessment of symptoms, such as with pulmonary function tests.

Mann et al.[117] and Gottlieb et al.[118] appear to be the most comprehensive articles on chronic effects of botulism, although there could be additional case reports that describe chronic botulism. Botulism, especially type A, leads to significant long-term effects that can last years. It is not anticipated that additional case reports would affect the anticipated severity and incidence of long-term botulism symptoms. Therefore, further literature analysis is not recommended at this time. This recommendation may be revisited in a few years if interest in potential long-term effects of botulinum injury continues and new papers related to the topic are published.

Conclusion: Botulism, especially type A, can lead to significant long-term complications. When acute symptoms are severe, symptoms including exercise intolerance (86%), weakness (83%), and difficulty speaking/breathing/swallowing (33%–83%) can last for 2 years or more. When acute symptoms are moderate, fewer long-term symptoms are reported, although weakness (~45%–66%) and exercise intolerance (~50%) are common symptoms.

Caveats:

- **Symptom frequencies are primarily derived from two papers, both of which used self-reporting rather than clinical data.**
- **Not all papers differentiated between botulinum toxin types.**
- **All of these cases are from foodborne botulism rather than aerosolized.**
- **All patients received at least some form of supportive care, if not botulinum antitoxins.**

K. Ricin

Ricin is a toxin produced by castor bean (*Ricinus communis*) that disrupts the synthesis of proteins.[119] Inhaled ricin causes lung damage, which can lead to death. There have been no reported cases of severe inhalational ricin exposure in humans. Therefore, chronic effects for ricin are difficult to determine. Bhaskaran et al.[120] subjected rhesus macaques to sublethal doses of ricin and followed the pathology. They found that if the macaques survived the initial exposure, they transitioned from an acute response to a subacute or chronic reparative process. In this subacute phase, there was repair of the pulmonary architecture

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[116] Mann et al., "Patient Recovery from Type A Botulism."

[117] Ibid.

[118] Gottlieb et al., "Long-Term Outcomes of 217 Botulism Cases."

[119] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 31-1.

[120] Manoj Bahaskaran et al., "Pathology of Lethal and Sublethal Doses of Aerosolized Ricin in Rhesus Macaques," *Toxicologic Pathology* 42, no. 3 (2014): 573–581, http://journals.sagepub.com/doi/pdf/10.1177/0192623313492248.

and clearing of alveolar spaces but persistent fibrosis.[121] This study, however, only lasted for 11 days, so true chronic effects could not be determined. McLain et al.[122] similarly found that although rabbits vaccinated with recombinant vaccines survived a lethal dose of ricin, most still had lung damage by the time they were sacrificed 95 days after respiratory challenge. Some of the lung injuries decreased between those sacrificed at 2 vs. 12 weeks, but many persisted. Lung injuries included mottled red lungs, reddened trachea, and non-collapsing lungs. Since no further papers could be found describing chronic effects of ricin exposure, no effects could be confirmed, and no further analysis would be recommended. If interest in potential chronic effects of ricin exposure continues, new experiments that followed unvaccinated animal models for a longer time after the initial acute illness would be required.

Conclusion: Although a single non-human primate study indicated that lung repair following ricin exposure may be a slow process, the experiment only lasted 11 days after exposure. A vaccine study also indicated that vaccinated animals still had lung damage 12 weeks after exposure. No information on potential long-term effects of ricin exposure is available at this time in unvaccinated animals followed for more than 2 weeks. New experiments would be required for this information.

L. Staphylococcal Enterotoxin B (SEB)

SEB is produced by the bacterium *Staphylococcus aureus.*[123] When SEB is inhaled, it produces fever, cough, nausea, and pain. Few cases of inhalational SEB exposure have been recorded. Nine patients were accidentally exposed to SEB[124] inhalationally, and all symptoms, including a lingering cough, resolved within 3 weeks of the end of the study. As stated in Section 2.F, no long-term effects (30 years later) were found in those exposed to SEB inhalationally in the Project Whitecoat Program either, although people exposed to SEB were not separated from those exposed to other agents or countermeasures.[125] Although the study by Ho-Chunk Technical Solutions[126] described papers on gene expression changes that may indicate long-term effects, these changes were only observed in the

[121] Ibid., 577.

[122] Daniel E. McLain et al., "Protective Effect of Two Recombinant Ricin Subunit Vaccines in the New Zealand White Rabbit Subjected to a Lethal Aerosolized Ricin Challenge: Survival, Immunological Response, and Histopathological Findings," *Toxicological Sciences* 126, no. 1 (1 March 2012): 72–83, https://doi.org/10.1093/toxsci/kfr274.

[123] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 32-1.

[124] Sheldon Sidell, "Human Clinical Syndrome Associated with Accidental Exposure to Aerosolized Staphylococcal Enterotoxin B," in *Special Report to Commission on Epidemiological Survey*, ed. H. G. Dangerfield, No. 65-FDS-1662 (Frederick, MD: Ft. Detrick, April 1965).

[125] Pittman et al., "An Assessment of Health Status among Medical Research Volunteers."

[126] Ho-Chunk Technical Solutions, "Assessment of Potential Long-Term Health Effects on Army Human Test Subjects."

first 3 hours of illness (no samples were taken after that). Since these changes only described acute effects and had no correlation to symptoms or protein analysis, they could not be used for any conclusions on long-term effects of SEB. No other descriptions of chronic effects have been found in humans or other animals nor have any studies followed solely individuals exposed to SEB for more than 3 weeks, so no further analysis would be recommended and at this time.

Conclusion: In one study of nine patients accidentally exposed to SEB inhalationally, none of the patients had chronic effects based on a follow-up of 3 weeks. No other studies have been found on long-term effects of SEB inhalation exposure, so no chronic effects have been described for this agent.

Caveats:

- **Only based on one paper of nine accidentally exposed individuals.**
- **Did not follow up with the individuals beyond 3 weeks.**

M. T-2 Mycotoxicosis

T-2 mycotoxins are produced by soil fungi of the *Fusarium* genus, and inhalation of these mycotoxins can cause pain, sneezing, weakness, dizziness, and loss of coordination.[127] No human cases of inhalational T-2 mycotoxicosis could be found in the literature. In addition, all animal cases showed an amelioration of symptoms within a few weeks and no chronic symptoms, although they were all sacrificed soon after.[128] In the absence of data, no conclusions on chronic effects of T-2 mycotoxicosis could be determined, and no further analysis would be recommended.

Conclusion: Although some animal studies indicated that animals given a non-lethal dose of T-2 mycotoxin recovered in the first few weeks, all animals were sacrificed soon afterwards. Therefore, no conclusions on potential long-term effects of ricin exposure could be determined at this time. New experiments would be required for this information.

[127] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 33-1–33-2.

[128] Victor F. Pang et al., "Experimental T-2 Toxicosis in Swine Following Inhalation Exposure: Effects on Pulmonary and Systemic Immunity and Morphologic Changes," *Toxicologic Pathology* 15, no. 3 (1987): 308–319, http://journals.sagepub.com/doi/pdf/10.1177/019262338701500309; D. A. Creasia et al., "Acute Inhalation Toxicity of T-2 Mycotoxin in Mice," *Fundamental and Applied Toxicology* 8, no. 2 (February 1987): 230–235, https://doi.org/10.1016/0272-0590(87)90121-7.

N. Conclusions

Several biological agents discussed in *AMedP-7.5*[129] can lead to significant long-term complications, while others appear to have no long-term effect or no information to determine whether there is an effect. This quick-look analysis determines the feasibility of describing potential long-term effects from 27 chemical and biological agents. Therefore, not only does this study briefly describe the long-term effects of each agent, it also indicates how much more information is available and which agents to prioritize if further study was performed.

The biological agents are divided into three groups for how much more information would potentially be available: no data, little data, or more data (see Table 2):

- No information on chronic effects was found for agents with "no data," either in animal or human studies, and no further analysis is warranted.
- For agents with "little data," few studies were found, and all were summarized in this report. Since this was a quick-look analysis, it is possible that a few other case reports are available that were not found in the initial search, but they would likely be small and not change the overall picture of chronic illness. Again, no further analysis is recommended, and conclusions are presented in each agent's section of the paper.
- For agents with "more data," only a subset of the papers on long-term effects was summarized in this analysis due to the breadth of information on the topic. IDA recommends further analysis of those agents with "more data" and significant long-term effects. Since only a subset of papers on long-term effects was analyzed, no formal conclusions were presented in those sections.

Table 2. Amount of Data Found for Biological Agents

No Data	Little Data	More Data
Ricin	Anthrax	Brucellosis
T-2 Mycotoxin	Glanders	Melioidosis
	Plague	Q Fever
	Tularemia	
	Smallpox	
	Encephalitides	
	Botulism	
	SEB	

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

The biological agents for which data on long-term effects was found were categorized further by the type of long-term effects observed (see Table 3). The categories were: no effect, mild effect, relapse, severe effect, or not applicable (N/A). In addition, the relative percent of people expected to show the effect was categorized into <3%, ~3%–50%, or >50%. These percentages are not exact, since, in many cases, people who recovered fully and had no long-term effects did not receive any follow-up after their illness(es) (although they could not be counted since they conceivably could have had a long-term effect that was not catalogued) and some agents, such as treated anthrax, had percentages based on fewer than 10 people.

Table 3. Effects of Biological Agents

Percent of Population with Long-Term Effect	No Effect	Mild Effect	Relapse	Severe Effect	N/A
<3% of cases				Smallpox	
				Q Fever (Un and Tr)	
~3%–50% of cases		Q Fever (Un and Tr)	Brucellosis (Un and Tr)	EEE	
		VEE	Glanders (Un and Tr)		
		WEE	Melioidosis (Un and Tr)		
		Tularemia (Un)			
>50% of cases	Plague (Tr)			Anthrax (Tr)	Anthrax (Un)
	SEB			Botulism (Un and Tr)	Plague (Un)
	Tularemia (Tr)				Ricin
					T-2

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

"Mild effect" was defined as an effect such as slight hand tremor that would not have a significant impact on the person's life or an effect that lasted less than 1 year and was not debilitating. "Relapse" was defined as an illness with periods of remission and relapse of the same symptoms, usually with the same severity, either in untreated or treated cases (even with proper use of antibiotics). "Severe effect" was defined as an illness with long-term effects lasting more than a year that would have a significant impact on quality of life or health resources (includes decreases in pulmonary function or cognitive defects). Not applicable ("N/A") was defined as illnesses for which there were no data on chronic effect or illnesses with a ~100% lethality. Illnesses were generally only included in one category,

unless there were two very distinct potential long-term effects. An example of an illness that was included in more than one category is Q fever, which can cause chronic fatigue syndrome, categorized as a mild effect for 3%–50% of people, or endocarditis, categorized as a severe effect for <3% of people. Some of these categories are subjective. Effects that were self-reported or may have a significant psychological component, such as chronic fatigue, are especially difficult to categorize.

3. Long-Term Effects of Chemical Agents

Information on the effects of chemical agents is generally found from intentional or accidental exposures to the agent through factory accidents, suicides, terrorist attacks, and other events. These scenarios of exposure can provide a useful source of knowledge on long-term symptoms. Many of these accidental or intentional exposures are well studied since they are generally unusual and attributable events. Unfortunately, the dose during almost any of these exposures is unknown and can only be estimated from the acute symptoms. In addition, since virtually none of these exposures are based on controlled studies, mild effects or delayed effects (such as cancer) are difficult to detect. This chapter discusses potential long-term effects of each of the chemical agents described in *AMedP-7.5*.[130] Since this paper is a quick-look analysis, only a small subset of the literature available is discussed for some of the agents. Agents with little literature available on long-term effects were described in the best detail possible, noting any gaps. A categorization of these agents for severity of long-term symptoms and the amount of literature still available on these agents is provided at the end of the chapter and in Chapter 4.

A. Nerve Agents

The neurological effects of nerve agents have been studied extensively, so only a small summary is presented here. Many incidents of nerve agent exposure or suspected nerve agent exposure have led the U.S. government to commission studies on the long-term effects. One notable example was the destruction of rockets containing sarin and cyclosarin at Khamisiyah, Iraq, during the Gulf War.[131] Although no one had acute symptoms of nerve agent exposure, later symptoms known as "Gulf war syndrome" emerged, leading to the question of whether low doses of nerve agents, such as those that were found at Khamisiyah, could produce these symptoms. Therefore, a committee was formed to review the literature on long-term effects of nerve agents.[132] This review provided a good foundation for the quick-look analysis of nerve agent effects, although additional resources were also reviewed for this short summary.

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[130] Oxford, *NATO Allied Medical Publication 7.5 (AMedP-7.5)*.

[131] Institute of Medicine, *Gulf War and Health: Updated Literature Review of Sarin*, 3.

[132] Ibid., 2.

Four major instances of sarin or other nerve agent exposure were examined in this quick-look analysis. The U.S. and UK militaries tested sarin or other nerve agents on servicemen who knowingly volunteered for the study.[133] The UK study used sarin, while the U.S. study used a variety of agents, including VX and sarin. None of the doses were lethal, although some service members did have acute effects of nerve agent exposure (which were promptly treated). No significant differences were found in mortality rates or major health effects between the U.S. servicemen exposed and those who served as controls at 5 or more years after exposure, besides a slight increase in malignant neoplasms (tumors that grow and metastasize).[134] The neoplasms, however, occurred randomly, and animal tests have not shown similar increases in tumors following nerve agent exposure. A survey conducted at least 25 years after the chemical weapon testing program found almost no statistically significant differences in health or psychologic symptoms between service members who were exposed and those who served as controls.[135] The only significant differences between the two groups were that those service members exposed to nerve agents had more frequent sleep problems, less frequent attention problems, and fewer instances of mortality. One difficulty with using the U.S. service member records to determine long-term effects was that many servicemen were exposed to multiple agents (including non-nerve agents) and the assignment to exposed or control groups was not random: the less healthy service members served as controls.[136] The analysis was also not set up to determine minor health effects, only major ones.

The British servicemen who were exposed to sarin at a dose of 15 milligram-minutes per cubic meter (mg-min/m^3) similarly had few long-term effects after acute symptoms of exposure.[137] The only long-term symptom of exposure was "jitter," a sign of potential failure of signal transmission between neurons and muscles. This effect was present at 3 hours and 1 year post-exposure but not 2 years post-exposure. No control was used in this experiment.[138]

Victims of industrial accidents with sarin or other nerve agents provide additional information on long-term effects. Among 77 people who were accidentally exposed at least once to toxic levels of sarin at least 1 year earlier, significant changes in sleep patterns

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[133] Ibid., 48–52.

[134] National Research Council, *Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents,* vol. 3, *Final Report: Current Health Status of Test Subjects* (Washington, DC: The National Academies Press, 1985), 28, https://doi.org/10.17226/9984.

[135] Institute of Medicine, *Gulf War and Health: Updated Literature Review of Sarin*, 48–49.

[136] Ibid., 49.

[137] Ibid., 49, 52.

[138] Ibid., 49

occurred, as measured with an electroencephalogram (EEG).[139] The exposed individuals had significantly more rapid eye movement (REM) (associated with dreaming) sleep than control individuals, although both groups had significantly less REM sleep than the average across other studies. This difference may have been due to the new environment that the subjects were in while their sleep was monitored.[140] Some other reviews of exposed workers found that they can have minor memory or emotional disorders over 6 months after the event.[141] In addition, two workers had long-term mild-to-moderate cerebral impairment from sarin, probably not from the sarin itself, but from the seizures that it caused, which is still relevant since high doses of nerve agent cause seizures.[142]

Survivors of the Tokyo subway sarin attacks and the Matsumoto sarin attack were monitored periodically for years after the attack, providing some insight on chronic effects of sarin in humans. In Matsumoto, one severely affected subject survived in a persistent vegetative state years after the attack.[143] As with the accidentally exposed workers, some had EEG abnormalities up to 5 years after the attacks. In those survivors who had severe symptoms from the Matsumoto attack, eye strain, fatigue, and weakness were more common than in those without symptoms.[144] Many victims noted similar symptoms in a survey distributed 5 years after the attack. This survey was answered by 655 subway victims who had varying initial symptom severities. Another test with rescue workers found no significant difference in neurobehavior 3 years after the subway attack between victims and controls.[145] Many survivors reported symptoms of post-traumatic stress disorder (PTSD), but this condition most likely did not arise from the sarin itself, but rather from being attacked by terrorists.

Organophosphate insecticide exposure has been even more extensively studied than nerve agent exposure but can sometimes produce different effects.[146] Therefore, for this

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[139] 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.

[140] Ibid.

[141] Duffy et al., "Long-Term Effects of an Organophosphate"; Mark A. Brown and Kelley A. Brix, "Review of Health Consequences from High-, Intermediate- and Low-Level Exposure to Organophosphorus Nerve Agents," *Journal of Applied Toxicology* 18, no. 6 (November/December 1998): 393–408, doi:10.1002/(SICI)1099-1263(199811/12)18:6<393::AID-JAT528>3.0.CO;2-0.

[142] Brown and Brix, "Review of Health Consequences from High-, Intermediate- and Low-Level Exposure."

[143] 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): 77, https://doi.org/10.1016/j.jns.2006.06.007.

[144] Ibid.

[145] Ibid., 82

[146] Institute of Medicine, *Gulf War and Health: Updated Literature Review of Sarin*, 30–32.

short study, effects of insecticide exposure are not discussed. A more extensive study of long-term effects from nerve agent exposure would include more information about these effects.

Although none of these studies were completely controlled experiments (and that sort of information is unlikely to be generated in humans in the future), they do suggest that chronic effects can occur and may be more likely for higher doses. The experiments on U.S. and UK servicemen used lower doses than experienced by many of the accidentally exposed workers and victims of the Japanese sarin attacks. Those experiments also had few noticeable long-term effects, while the other victims had some reports of psychological or sleep changes as well as some fatigue and eye pain. Since almost none of these studies reported the dose, no exact dose-effect models could be determined. In addition, all of these victims were treated. Further analysis would be needed to review more recent studies on the effects of nerve agents, including data from the Iran-Iraq War and the effects of other nerve agents beyond sarin. In addition, further analysis, especially of animal studies, is recommended to determine more precise dose effects and whether untreated victims have different long-term effects. The long-term effects of seizures and other symptoms of severe acute nerve agent exposure would also be studied.

B. Sulfur Mustard (HD)

The long-term effects of sulfur mustard have been extensively studied, so only a short summary is provided here. Two major sources of information about the effects of sulfur mustard are included in this quick-look analysis: a 1993 study[147] performed for the Veterans Administration on the long-term effects of sulfur mustard and some studies from the Iran-Iraq War. Acute symptoms of sulfur mustard exposure include skin itching and burning, eye irritation and conjunctivitis, and pulmonary symptoms including difficulty breathing, coughing, chest tightness, and lung collapse. The long-term effects of sulfur mustard are generally split into three categories (lung, skin, and eye injuries), same as the acute effects. In addition, lung and skin cancer have been investigated as being linked to sulfur mustard exposure. Overall, mortality rates did not change much between those dosed with sulfur mustard in U.S. testing,[148] but that finding did not mean that people did not have long-term complications from injuries. One difficulty with the long-term effects of sulfur mustard is that acute symptoms are often not recorded (especially in large studies) and many of the long-term effects are commonly observed in control populations (cancer,

[147] Institute of Medicine, *Veterans at Risk*, 47.

[148] Institute of Medicine, *Veterans at Risk*; 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, cough, and so forth). Therefore, some values are given in ratios compared to a control.

Lung injury is the most common long-term complication reported following sulfur mustard injury. Veterans of the Iran-Iraq War who were exposed to HD had high rates of chronic bronchitis and other chronic respiratory conditions, ranging from 42.5%–80%.[149] One study found that 4 of 10 people who were exposed to HD had chronic bronchitis 11 years after the incident.[150] Another study found a rate of chronic bronchitis of over 50%.[151] Unfortunately, these studies did not have a control group to which to compare the rates. Other common respiratory concerns included lung lesions, asthma, frequent infections, cough, difficulty breathing, and wheezing. These symptoms were noted even 20 years after initial exposure, indicating that they did not pass with time. At 3 years, one study found that 80% of exposed Iranian veterans had cough, expectoration, and trouble breathing.[152] Again, no controls were included in this paper. Most of the symptoms were mild.[153]

Studies of HD exposures previous to the Iran-Iraq war also found significant respiratory complications. In a study of 89 people gassed with HD during World War I, 27 (30.3%) had residual effects including chronic bronchitis, emphysema, and asthma.[154] Another study found a significant increase in bronchitis and respiratory diseases in sulfur mustard factory workers.[155] In addition, the association of sulfur mustard exposure and lung cancer incidence has been studied extensively. Sulfur mustard is a known carcinogen,[156] but, compared to smoking and other factors, it is often difficult to separate it as a cause of lung cancer.[157] Cancer of the larynx was more common among factory workers

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[149] 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; M. Balali-Mood, S. H. Mousavi, and B. Balali-Mood, "Chronic Health Effects of Sulphur Mustard Exposure with Special Reference to Iranian Veterans," *Emerging Health Threats Journal* 1 (2008): e7, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3167581/.

[150] 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.

[151] Khateri et al., "Incidence of Lung, Eye, and Skin Lesions as Late Complications."

[152] M. Balali-Mood, Mousavi, and B. Balali-Mood, "Chronic Health Effects of Sulphur Mustard Exposure."

[153] Khateri et al., "Incidence of Lung, Eye, and Skin Lesions as Late Complications."

[154] Institute of Medicine, *Veterans at Risk*, 121.

[155] Ibid., 119–120.

[156] Ibid., 81–104.

[157] 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.

exposed to HD than it was among the controls, but these workers were generally exposed over years rather than in a single attack.[158] One study of Iranian soldiers found a twofold higher risk of lung cancer among exposed nonsmokers than among control nonsmokers but no effect of exposure among smokers.[159] Further study would be needed to make a more definitive link between acute sulfur mustard exposure and cancer.

Sulfur mustard causes acute burns on the body, some of which can be severe. These burns can lead to long-term scarring, lesions, and other skin defects that can last a lifetime. Skin lesions are incredibly common at HD burn sites. One study of 34,000 Iranian soldiers found that 24.5% of those exposed to HD had skin lesions.[160] Most of these lesions were mild. Another study of Iranian civilians found that 84.5% of those initially hospitalized after exposure to HD had skin lesions, compared to 69.6% of those exposed but not hospitalized and 55.5% of controls.[161] Other skin conditions associated with HD exposure include itching, burning, hyperpigmentation, and dry skin.[162] Nerve damage can also occur. In 10 people exposed to HD in the Iran-Iraq War, all of them had pain and damage in their limbs (where they were burned) and over half had short-term memory impairment and/or intermittent cold and warm feelings.[163] These symptoms were thought to have been from the burns rather than the HD itself. There may also be an association between HD burns and skin cancer.[164]

Long-term eye effects are less common but can be quite severe and lead to chronic decreases in vision. Acute eye effects are very common for sulfur mustard, but most of these injuries resolve over time. Long-term eye effects generally fall into two categories: chronic and delayed-onset.[165] In a study of 48 Iranian patients with keratitis from mustard gas, 31 (64.6%) had chronic symptoms that remained from the time of acute exposure to years later, and 17 (35.4%) had delayed-onset symptoms that went away initially and then returned 1 to 15 years later. Most of the symptoms included decreased vision from corneal

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158 Institute of Medicine, *Veterans at Risk*, 97–101.

159 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.

160 Khateri et al., "Incidence of Lung, Eye, and Skin Lesions as Late Complications."

161 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.

162 Ibid.

163 Thomsen et al., "Chronic Neuropathic Symptoms after Exposure to Mustard Gas."

164 Institute of Medicine, *Veterans at Risk*, 168.

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

defects (especially scars or opacities), dry eye, and eye irritation. These symptoms would likely not occur naturally with age (many of those with delayed effects were in their twenties when exposed). Some patients did have surgery to correct impairments but still generally had 20/80 vision afterwards.[166] Other chronic eye symptoms include eye lesions,[167] conjunctivitis, and photophobia.[168] Occasionally, people have reported that HD exposure results in permanent blindness.[169]

Sulfur mustard has been associated with many long-term effects, including chronic bronchitis, lung cancer, cough, skin lesions, itching, and other skin conditions, and chronic eye irritation and progressive visual deterioration. Many of these effects have been described in veterans of the Iran-Iraq War and World War I. This quick-look analysis only examined some of the literature on sulfur mustard, and a further analysis would be needed to determine more precise dose effects and rates of occurrence. More information from the Iran-Iraq War and potentially more information from factory and other exposure were not analyzed in this paper. Most of the documents on long-term effects of HD found in this quick-look analysis did not include the severity of acute effects or initial treatment. Further study is needed to find more documents that may have that information.

C. Phosgene (CG)

Phosgene causes short-term lung damage, but little is known about long-term effects of phosgene. Most people fully recover within the first few weeks,[170] and a study in rats similarly found no persistent change in lung tissue 3 months after exposure.[171] A few people complain of difficulty breathing after exertion or exercise for less than 3 years after phosgene exposure.[172] A study of six individuals who had acute symptoms of phosgene exposure while working in a factory 3–14 months before found that all six had slight

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166 Ibid.

167 Khateri et al., "Incidence of Lung, Eye, and Skin Lesions as Late Complications."

168 Thomsen et al., "Chronic Neuropathic Symptoms after Exposure to Mustard Gas."

169 Institute of Medicine, *Veterans at Risk*, 140–141.

170 Werner F. Diller, "Late Sequelae after Phosgene Poisoning: A Literature Review," *Toxicology and Industrial Health* 1, no. 2 (October 1985): 129–136, https://www.ncbi.nlm.nih.gov/pubmed/3842186.

171 J. Pauluhn et al., "Workshop Summary: Phosgene-Induced Pulmonary Toxicity Revisited: Appraisal of Early and Late Markers of Pulmonary Injury from Animal Models with Emphasis on Human Significance," *Inhalation Toxicology* 19, no. 10 (August 2007): 789–810, https://www.ncbi.nlm.nih.gov/pubmed/17687713.

172 Diller, "Late Sequelae after Phosgene Poisoning"; Jonathan Borak and Werner F. Diller, "Phosgene Exposure: Mechanisms of Injury and Treatment Strategies," *Journal of Occupational and Environmental Medicine* 43, no. 2 (February 2001): 110–119, https://www.ncbi.nlm.nih.gov/pubmed/11227628.

changes in lung function and that most had rapid, shallow breathing.[173] The changes in lung function were more apparent in the five patients who had been injured 3–6 months before the experiment than the patient injured 14 months prior. Three individuals had shortness of breath following exercise, some chest pain, and non-specific symptoms.[174] No correlation between estimated phosgene dose and long-term effects has been found, although long-term effects do tend to increase with smoking.[175] A study of 338 workers who accidentally inhaled 10–159 ppm-minutes (41–617 mg-min/m^3, with 250 mg-min/m^3 being the concentration-time estimated to produce severe effects in 50% of the population ($ECt_{50\text{-}severe}$)[176]), mostly on the lower side of the range, found no relationship between phosgene exposure and symptoms lasting over 30 days.[177] None of these studies have been large enough or found enough evidence of long-term effects to produce effective measurements of rate of symptoms.

The long-term effects described are rare, and few studies have been performed on them. Therefore, the IDA team determined that long-term effects, including slight changes in lung function, especially after exertion, may occur after phosgene exposure, but no precise information was found on rate of occurrence or relationship between rate of occurrence and dose. Since no other papers could be found describing chronic effects of phosgene exposure, no further analysis is recommended.

Conclusion: Although most individuals recover fully from phosgene exposure within the first 30 days after exposure, some individuals have reported difficulty breathing following exercise or exertion or slight changes in lung function for up to 3 years after acute intoxication. Smoking may exacerbate these effects. Not enough information is known to determine rate of illness, but, based on the lack of long-term effects observed in animals and in relatively large (338 workers) studies on accidental phosgene exposures, the rate is likely small. In addition, no correlation could be found between initial phosgene dose and severity of symptoms.

Caveats:

- **Almost all of the descriptions of long-term effects have been from case reports, therefore making it difficult to determine rate of illness.**
- **All accidental exposures did not include an initial dose estimate.**

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[173] Morton Galdston et al., "A Study of the Residual Effects of Phosgene Poisoning in Human Subjects. I. After Acute Exposure," *Journal of Clinical Investigations* 26, no. 2 (March 1947): 145–168, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC435656/.

[174] Ibid.

[175] Diller, "Late Sequelae after Phosgene Poisoning."

[176] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 8-7–8-11.

[177] James J. Collins et al., "Results from the US Industry-Wide Phosgene Surveillance: The Diller Registry," *Journal of Occupational and Environmental Medicine* 53, no. 3 (March 2011): 239–244, https://www.ncbi.nlm.nih.gov/pubmed/21293301.

D. Chlorine (Cl_2)

Chlorine is a commonly used industrial chemical and is the second-most common cause of serious accidents from toxic chemical release.[178] Many of these accidents have been documented extensively and included follow-ups years after the exposure. Acute chlorine exposure causes lung damage and difficulty breathing.[179] Results from long-term follow-up of exposed victims have been mixed. Some have found significant defects in lung function and/or asthma for years after the exposure, while others have found no such effects a month or more after the injury.[180] Smokers, older people, and those with asthma or previous allergies were more likely to have long-term effects than healthy individuals. Since all of the studies that characterized the long-term effects of chlorine exposure were from accidents, no information was available on the acute dose received by each individual.

The most commonly described long-term effects of chlorine exposure were decreases in lung capacity and Reactive Airways Dysfunction Syndrome (RADS), which is a form of asthma that arises from an acute irritant exposure.[181] In a review of studies before 1980 on long-term effects of chlorine, few had long-term effects, although some studies reported reduced lung capacity over time, especially in people who smoked.[182] When 13 people exposed to chlorine gas in 1975 were followed up periodically for 12 years after the exposure, 67% had persistent airflow obstruction and 38% had increased airway reactivity throughout the time period.[183] Almost all of the people exposed were smokers or ex-smokers but had been healthy before the accident. There was no non-exposed control group nor a significant number of non-smokers to which to compare the results. The results suggest, however, that among smokers, lung effects can last for many years after the initial accident. Some studies have found that the estimated initial exposure dose is positively correlated to the presence of long-term effects.[184] A year after a large chlorine gas spill from a train in Graniteville, South Carolina, the 1,807 mill workers tested had significant

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[178] Richard B. Evans, "Chlorine: State of the Art," *Lung* 183, no. 3 (June 2005): 151–167, https://link.springer.com/article/10.1007%2Fs00408-004-2530-3.

[179] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 9-3.

[180] Evans, "Chlorine: State of the Art."

[181] 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/.

[182] 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.

[183] David A. Scwartz, 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.

[184] Rupali Das and Paul D. Blanc, "Chlorine Gas Exposure and the Lung: A Review," *Toxicology and Industrial Health* 9, no. 3 (May–June 1993): 439–455, https://www.ncbi.nlm.nih.gov/pubmed/8367885.

decreases in lung capacity relative to their results before the accident, although lung capacity improved slightly after another 6 months.[185] This study only looked at those workers who had stayed with the mill after the accident—so may have omitted those with more serious injuries—and assumed that all who were working at the mill on the day of the accident were exposed to chlorine.

Treatment may alleviate some of the long-term effects of chlorine exposure. In a comparison of two sisters exposed to chlorine in the same accident, the sister who received corticosteroids in her initial treatment had normal lung function 2 years afterwards, while the sister who did not receive corticosteroids had persistent abnormalities in lung function 2 years afterwards.[186] Both sisters smoked a third of a pack a day. Another study of a nonsmoking 36-year-old with chronic asthma who was exposed to chlorine found that symptoms reappeared after steroids were stopped 5 weeks after exposure. However, after steroids were restarted, lung function improved at 3 and 5 months after the accident.[187] Both of these studies were on single individuals, so an actual systematic review would be needed to better understand the relationship between steroid treatment and long-term effects of chlorine exposure.

Chlorine does appear to have long-term effects in some populations, especially smokers, although the exact nature of that association is not clear. The most common long-term symptoms from chlorine exposure were decreases in lung capacity, increases in airway reactivity, and asthma. Since all of the studies reviewed for this quick-look analysis were from accidents, no information was available about chlorine dose. This study also included only a subset of chlorine exposure data. IDA recommends a more thorough analysis of chlorine exposure studies as well as potential animal studies of long-term effects to produce a clearer picture of the effects of chlorine on long-term lung health.

E. Ammonia (NH_3)

Ammonia is the most commonly used toxic industrial chemical (TIC) and can produce acute symptoms of lung dysfunction, difficulty breathing, and eye irritation.[188] Although most descriptions of injuries following ammonia spills do not include any

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[185] Kathleen A. Clark et al., "Lung Function before and after a Large Chlorine Gas Release in Graniteville, South Carolina," *Annals of the American Thoracic Society* 13, no.3 (March 2016): 356–363, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5015716/.

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

[187] 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.

[188] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 10-1.

long-term effects, some individuals who had more severe acute symptoms later developed respiratory or ocular defects that lasted for years after the event.[189] Most of the long-term effects that were described have been respiratory, although one individual who was sprayed in the face with ammonia in a fertilizer accident was permanently blinded,[190] and another individual had decreased vision for at least a year after receiving corneal burns from anhydrous ammonal fumes.[191] Many chemicals can cause ocular damage when splashed in the eye, so this is not unique to ammonia. Rinsing the eyes quickly, which these individuals did not do, may prevent this permanent disability.

Long-term respiratory effects were described in some individuals following exposure, especially among smokers. There were high rates of smoking among workers in some of the accidents, however, so non-smoking controls were not always available. In five individuals severely exposed to ammonia in an ammonia plant between 1966 and 1967, the person who quit smoking afterwards had no sequelae, while two of the four smokers had significant reductions in breathing capacity for at least 5 years after the accident.[192] Two of three people who had persistent respiratory symptoms 2 years after severe ammonia exposure were smokers.[193] The non-smoker had restrictive lung disease, while the two smokers had wheezing and persistent difficulty breathing. Non-smokers can also have chronic cough and bronchial infections for up to 10 years after a severe accident.[194]

These long-term effects generally occurred after severe ammonia exposure and almost all were due to respiratory damage that never healed completely. No other papers were found describing long-term effects from severe exposures, and no papers were found on long-term effects following mild or moderate exposures. In addition, so few papers were found (almost all describing case reports) that no rates of long-term symptoms could be determined. Therefore, a more thorough analysis would not be recommended due to the

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[189] James E. Lessenger, "Anhydrous Ammonia Injuries," *Journal of Agromedicine* 3, no. 3 (1996): 13–26, http://www.tandfonline.com/doi/pdf/10.1300/J096v03n03_03.

[190] Donald M. Levy et al., "Ammonia Burns of the Face and Respiratory Tract," *Journal of the American Medical Association* 190, no. 10 (December 7, 1964): 873–876, https://jamanetwork.com/journals/jama/article-abstract/1165659?redirect=true.

[191] Irving Kass et al., "Bronchiectasis Following Ammonia Burns of the Respiratory Tract: A Review of Two Cases," *Chest* 62, no. 3 (September 1972): 282–285, https://doi.org/10.1378/chest.62.3.282.

[192] M. Walton, "Industrial Ammonia Gassing," *British Journal of Industrial Medicine* 30, no. 1 (January 1973): 78–86, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1009482/.

[193] Rafael E. de la Hoz, Donald P. Schueter, and William N. Rom, "Chronic Lung Disease Secondary to Ammonia Inhalation Injury: A Report on Three Cases," *American Journal of Industrial Medicine* 29, no. 2 (February 1996): 209–214, http://onlinelibrary.wiley.com/doi/10.1002/(SICI)1097-0274(199602)29:2%3C209::AID-AJIM12%3E3.0.CO;2-7/abstract.

[194] D. Leduc et al., "Acute and Long Term Respiratory Damage following Inhalation of Ammonia," *Thorax* 47, no. 9 (September 1992): 755–757, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC474816/; Kass et al., "Bronchiectasis Following Ammonia Burns of the Respiratory Tract."

lack of data, although individuals severely exposed to ammonia may need to be monitored for years after the event due to potential respiratory difficulties.

Conclusion: Some individuals, especially smokers, have significant reductions in breathing capacity, difficulty breathing, and chronic cough for up to 10 years after severe ammonia exposure. These effects have only been observed in those with severe acute symptoms. No reports of long-term effects were found following mild or moderate ammonia exposures. In addition, two people who did not wash their eyes soon after being sprayed with ammonia were permanently blinded or vision impaired.

Caveats:

- **Only 10 case reports were found describing chronic effects of ammonia exposure.**
- **No information on potential long-term effects from mild or moderate exposures.**
- **Most accidental exposures did not include an initial dose estimate.**
- **All data was from case reports, so rate of symptoms could not be determined.**

F. Hydrogen Cyanide (AC)

Hydrogen cyanide is a blood agent and also a TIC. Most of the data on symptoms of hydrogen cyanide exposure in humans is from attempted or successful suicide, usually by ingestion. Cyanide inhibits a protein involved in the generation of adenosine triphosphate (ATP) and therefore arrests cellular metabolism.[195] Acute symptoms from cyanide exposure include shortness of breath, vomiting, drowsiness, muscle spasms, weakness, and dizziness. Many reports have found long-term neurologic sequelae following exposure to large doses of cyanide. The long-term effects are likely from brain damage since hydrogen cyanide affects the availability of oxygen in the brain.[196] Almost all of these reports are from single cases of attempted suicide with cyanide salts or accidental inhalation of hydrocyanic acid fumes. All of the reports discussing long-term sequelae (or lack thereof) of acute cyanide exposure have been assembled in Table 4 to show the potential rate of occurrence and symptoms of neurological sequelae. In addition, the severity of initial symptoms, defined by the severity levels used in *AMedP-7.5*[197] are included. Briefly, people who had mild symptoms were designated Severity 1. Those with moderate symptoms, equivalent to what would be treated on an outpatient bases, were designated as Severity 2. Those who had severe symptoms and were treated on an inpatient basis but did not have life-threatening symptoms (such as loss of breathing) were designated as Severity 3. If anyone was put on artificial respiration, he or she was designated as Severity 4. No people with mild symptoms (Severity 1) had systemic effects, so those people are not included in the table.

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[195] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 11-1.

[196] Thomas H. Milby and Randall C. Baselt, "Hydrogen Sulfide Poisoning: Clarification of Some Controversial Issues," *American Journal of Industrial Medicine* 35, no. 2 (February 1999): 192–195, doi:10.1002/(SICI)1097-0274(199902)35:2<192::AID-AJIM11>3.0.CO;2-C.

[197] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 2-4.

Table 4. Outcomes of Cases of Cyanide Exposure

Patient #	Exposure or Acute Effects Info	Outcome	Severity of Sequelae	Source
1	HCN fumes, Severity 4	Mild writhing movements of hands and personality changes	Severe	Chen and Rose (1952)[198]
2	HCN fumes, Severity 2	Felt weak for one month	–	Chen and Rose (1952)
3	HCN fumes, Severity 4	No sequelae	–	Chen and Rose (1952)
4	1.5 g NaCN, Severity 4	no sequelae	–	De Busk and Seidl (1969)[199]
5	4-6 g KCN, Severity 4	No sequelae	–	De Busk and Seidl (1969)
6	200 mg KCN, Severity 4	No sequelae	–	Graham et al. (1977)[200]
7	KCN, Severity 3	No sequelae	–	Vogel, Sultan. and Ten Eyck (1981)[201]
8	KCN, Severity 4	No sequelae	–	Brivet et al. (1983)[202]
9	500 mg/m^3 for 6 min HCN fumes, Severity 4	Slight loss in peripheral vision	Mild	Bonsall (1984)[203]
10	KCN, Severity 4	No sequelae	–	Johnson Hall, and Rumack (1989)[204]

[198] K. K. Chen and Charles L. Rose, "Nitrite and Thiosulfate Therapy in Cyanide Poisoning," *Journal of the American Medical Association* 149, no. 2 (May 10, 1952): 113–119, doi:10.1001/jama.1952.02930190015004.

[199] Robert F. De Busk and Larry G. Seidl, "Attempted Suicide by Cyanide: A Report of Two Cases," *California Medicine* 110, no. 5 (May 1969): 394–396, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1503494/.

[200] David L. Graham et al., "Acute Cyanide Poisoning Complicated by Lactic Acidosis and Pulmonary Edema," *Archives of Internal Medicine* 137, no. 8 (September 1977): 1051–1055, doi:10.1001/archinte.1977.03630200055016.

[201] Stephen N. Vogel, Thomas R. Sultan, and Raymond P Ten Eyck, "Cyanide Poisoning," *Clinical Toxicology* 18, no. 3 (1981): 367–383, https://doi.org/10.3109/15563658108990043.

[202] F. Brivet et al., "Acute Cyanide Poisoning: Recovery with Non-specific Supportive Therapy," *Intensive Care Medicine* 9, no. 1 (1983): 33–35, https://link.springer.com/content/pdf/10.1007/BF01693704.pdf.

[203] J. L. Bonsall, "Survival without Sequelae Following Exposure to 500 mg/m^3 of Hydrogen Cyanide," *Human & Experimental Toxicology* 3, no. 1 (1984): 57–60, http://journals.sagepub.com/doi/abs/10.1177/096032718400300108 1.

[204] Walter S. Johnson, Alan H. Hall, and Barry H. Rumack, "Cyanide Poisoning Successfully Treated without 'Therapeutic Methemoglobin Levels,'" *The American Journal of Emergency Medicine* 7, no. 4 (July 1989): 437–440, https://doi.org/10.1016/0735-6757(89)90057-0.

Patient #	Exposure or Acute Effects Info	Outcome	Severity of Sequelae	Source
11	800 mg KCN, Severity 4	Severe parkinsonian symptoms	Severe	J. M. Feldman and M. D. Feldman (1990)[205]
12	1 g KCN, Severity 4	Severe muscle contractions, difficulty walking and talking, resolving after 38 days; mild muscle contractions for at least 21 years afterwards	Severe	Valenzuela, Court, and Godoy (1992)[206]
13	100 mg KCN, Severity 3	Bo sequelae except vague numbness in left knee	Mild	Saincher, Swirsky, and Tenenbein (1994)[207]
14	300 mg KCN, Severity 3	One month no symptoms, then gradual progressive weakness, slurred speech, and muscle contractions, leaving her bedridden for 5 years	Severe	Borgohain et al. (1995)[208]
15	"Cyanide" ingestion, Severity 4	5 month follow-up: hair loss, short term memory difficulty, and intermittent stiffness of limbs	Severe	Chin and Calderon (2000)[209]
16	HCN fumes, Severity 3	1 year follow-up: mild impairment in memory and concentration, confirmed by neurological testing	Mild	Lam and Lau (2000)[210]
17	HCN fumes, Severity 2	No sequelae	–	Lam and Lau (2000)

[205] Jacqueline M. Feldman and Marc D. Feldman, Sequelae of Attempted Suicide by Cyanide Ingestion: A Case Report," *International Journal of Psychiatry in Medicine* 20, no. 2 (1990): 173–179, http://journals.sagepub.com/doi/pdf/10.2190/2XVU-MGTC-RUMJ-JY7X.

[206] Raúl Valenzuela, Jaime Court, and Jaime Godoy, "Delayed Cyanide Induced Dystonia," *Journal of Neurology, Neurosurgery, and Psychiatry* 55, no. 3 (March 1992): 198–199, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1014725/.

[207] Anurag Seincher, Neil Swirsky, and Milton Tenenbein, "Cyanide Overdose: Survival with Fatal Blood Concentration without Antidotal Therapy," *The Journal of Emergency Medicine* 12, no. 4 (July–August 1994): 555–557, https://doi.org/10.1016/0736-4679(94)90359-X.

[208] Rupam Borgohain et al., "Delayed Onset Generalized Dystonia after Cyanide Poisoning," *Clinical Neurology and Neurosurgery* 97, no. 3 (August1995): 213–215, https://doi.org/10.1016/0303-8467(95)00029-J.

[209] Robert G. Chin and Yvette Calderon, "Acute Cyanide Poisoning: A Case Report," *The Journal of Emergency Medicine* 18, no. 4 (May 2000): 441–445, https://doi.org/10.1016/S0736-4679(00)00161-X.

[210] K. K. Lam and F. L. Lau, "An Incident of Hydrogen Cyanide Poisoning," *The American Journal of Emergency* Medicine 18, no. 2 (March 2000): 172–175, https://doi.org/10.1016/S0735-6757(00)90012-3.

Patient #	Exposure or Acute Effects Info	Outcome	Severity of Sequelae	Source
18	KCN ingestion, Severity 3	No sequelae	–	Weng et al. (2004)[211]
19	"Cyanide" intravenous, Severity 3	No sequelae	–	Prieto et al. (2005)[212]
20	KCN ingestion, Severity 4	Significant brain damage, leading to severe muscle stiffness and contractions and difficulty swallowing and speaking for at least 2 months afterwards	Severe	Zaknun et al. (2005)[213]
21	KCN ingestion, Severity 2	No sequelae	–	Borron et al. (2007)[214]
22	KCN ingestion, Severity 4	No sequelae	–	Borron et al. (2007)
23	CN salt unknown intoxication, Severity 4	Memory impairment	Severe	Borron et al. (2007)
24	KCN ingestion, Severity 3	No sequelae	–	Borron et al. (2007)
25	KCN ingestion, Severity 2	No sequelae	–	Borron et al. (2007)
26	Cyanogen bromide inhalation, Severity 2	No sequelae	–	Borron et al. (2007)
27	HgCN ingestion, Severity 2	No sequelae	–	Borron et al. (2007)
28	KCN ingestion, Severity 4	No sequelae	–	Borron et al. (2007)

[211] Te-I Weng et al., "Elevated Plasma Cyanide Level after Hydroxocobalamin Infusion for Cyanide Poisoning," *The American Journal of Emergency Medicine* 22, no. 6 (October 2004): 492–493, http://dx.doi.org/10.1016/j.ajem.2004.06.004.

[212] I. Prieto et al., "Acute Cyanide Poisoning by Subcutaneous Injection," *Emergency Medicine Journal* 22, no. 5 (May 2005): 389–390, doi:10.1136/emj.2004.016915.

[213] John J. Zaknun et al., "Cyanide-Induced Akinetic Rigid Syndrome: Clinical, MRI, FDG-PET, β-CIT and HMPAO SPECT Findings," *Parkinsonism & Related Disorders* 11, no. 2 (March 2005): 125–129, https://doi.org/10.1016/j.parkreldis.2004.07.013.

[214] Stephen W. Borron et al., "Hyrdoxocobalamin for Severe Acute Cyanide Poisoning by Ingestion or Inhalation," *The American Journal of Emergency Medicine* 25, no. 5 (June 2007): 551–558. https://doi.org/10.1016/j.ajem.2006.10.010.

Patient #	Exposure or Acute Effects Info	Outcome	Severity of Sequelae	Source
29	KCN ingestion, Severity 2	No sequelae	–	Borron et al. (2007)
30	25 g KCN ingestion, Severity 4	No sequelae	–	Fortin (2010)[215]

Note: CN = cyanide, HCN = hydrogen cyanide, HgCN = mercury cyanide, KCN = potassium cyanide, NaCN = sodium cyanide.

Out of these 30 instances, 10 patients had long-term sequelae (33%). Because many other reports do not include information beyond the acute phase of disease, it is possible that the 33% incidence from 30 cases misrepresents the truth; however, it is impossible to know without additional data. In addition, those patients with more severe acute symptoms were more likely to have long-term sequelae.

Of the seven patients with moderate acute symptoms (Severity 2), none (0%) had symptoms lasting longer than 1 month. Of the seven patients with severe acute symptoms (Severity 3), four had no sequelae, two had mild sequelae, and one had severe sequelae (28.6% mild, 14.3% severe). The mild sequelae included numbness in the knee and mild impairment in memory and concentration. The patient with severe sequelae had gradual progressive weakness, slurred speech, and muscle contractions, leaving her bedridden for 5 years.[216] Of the 16 patients with very severe acute symptoms (Severity 4), 9 had no sequelae, 1 had mild sequelae, and 6 had severe sequelae (6.3% mild, 37.5% severe). The patients with mild sequelae had a slight loss in peripheral vision. Severe sequelae included personality changes, muscle contractions, severe parkinsonian symptoms, and memory impairment. Not enough information was available on the length of the period of hypoxia and/or seizures in patients to determine whether it was correlated to severity of sequelae. None of the patients with mild acute symptoms were reported as having or not having long-term symptoms. Therefore, we would anticipate no long-term symptoms following initial exposures that produced mild or moderate acute symptoms but an approximately 40% chance of long-term symptoms (more severe symptoms anticipated following more severe acute symptoms) following initial exposures that produced severe or very severe acute symptoms. No information was found on untreated patients, so no conclusions could be made about long-term effects following untreated exposure to hydrogen cyanide.

No more papers were found describing long-term effects of hydrogen cyanide. Therefore, further literature analysis is not recommended at this time. This recommendation may

[215] Jean-Luc Fortin et al., "Hydroxocobalamin for Poisoning Caused by Ingestion of Potassium Cyanide: A Case Study," *The Journal of Emergency Medicine* 39, no. 3 (September 2010): 320–324, https://doi.org/10.1016/j.jemermed.2008.04.040.

[216] Borgohain et al., "Delayed Onset Generalized Dystonia."

be revisited in a few years if interest in potential long-term effects of hydrogen cyanide injury continues and new papers related to the topic are published.

Conclusion: No reports of long-term symptoms were found following exposures producing mild or moderate acute symptoms. In addition, no reports were found on untreated exposures to cyanide. Following exposures producing severe or very severe acute symptoms, however, neurological sequelae are common (~40% of 23 cases described). Severe or very severe acute symptoms can produce hypoxia in the brain and lead to brain damage. These sequelae can range from mild (slight loss in peripheral vision or occasional numbness of the knee) to very severe (muscle contractions, bedridden, memory impairment, and/or personality changes), lasting years.

Caveats:

- **Only 30 case reports were found describing chronic effects of cyanide exposure.**
- **Almost all were based on ingestion of cyanide salts (although the symptom profile is identical between ingestion and inhalation).**
- **All patients were treated.**

G. Cyanogen Chloride (CK)

Cyanogen chloride is made up of a cyanide moiety (C≡N) and a chlorine moiety (–Cl), and the agent produces symptoms similar to those observed for each of those compounds separately (hydrogen cyanide and chlorine gas). These symptoms include shortness of breath, paralysis, eye and airway irritation, and muscle spasms. In large doses, the effects from cyanide are the most damaging.[217] Only one description of human symptoms following severe cyanogen chloride exposure was found.[218] All others only detailed symptoms that followed very low doses, and no long-term symptoms were found. A 22-year-old woman was found unconscious and given amyl nitrite and sodium nitrite. She was sent to a hospital and given additional supportive care before returning home the next day. She was not monitored for later sequelae.

Some animal experiments described "delayed symptoms" from cyanogen chloride, but all of these symptoms lasted, at the most, 1 month.[219] These delayed symptoms, typically observed in dogs and monkeys, included cough and paralysis. Cough generally resolved within 5 to 10 days and was often related to secondary bacterial infection.[220] Animals with paralysis typically died 3 to 5 days after the initial acute exposure (one recovered after 25 days), but these animals were also given no supportive care. If supportive care had been given, neurological sequelae, such as that observed in hydrogen

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[217] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 12-2.

[218] Chen and Rose, "Nitrite and Thiosulfate Therapy in Cyanide Poisoning."

[219] Julius M. Coon, George J. Rotariu, and Drusilla VanHoesen, *Cyanogen Chloride: Special Toxicity Studies*, ORSD-5001 (Chicago, IL: University of Chicago Toxicity Laboratory, March 31, 1945).

[220] Ibid.

cyanide patients (see Section 3.F), may have been observed since the two compounds share a mechanism of action. Since acute symptoms of cyanogen chloride typically mirror those of hydrogen cyanide at high doses, long-term symptoms may be the same. However, with no human data or treated data, that assumption could not be confirmed.

No more papers that described long-term effects of cyanogen chloride were found, and none were found that described effects that lasted longer than 2 weeks after exposure. Therefore, further literature analysis is not recommended at this time. This recommendation may be revisited in a few years if interest in the potential long-term effects of cyanogen chloride injury continues and new papers related to the topic are published.

Conclusion: No descriptions of long-term symptoms following acute cyanogen chloride exposure in humans were found. In animal studies, some animals had delayed paralysis or cough following exposure, although no symptoms were followed more than 3 weeks after exposure. All animals except one died after paralysis, and none were given supportive care. The paralysis was similar to that following hydrogen cyanide exposure. Cough was typically associated with secondary bacterial infection. Due to the lack of data, no rates could be determined. Since cyanogen chloride has almost the same mechanism of action as hydrogen cyanide, we assume that the same effects would occur for the two agents. Therefore, following exposures that produce severe or very severe acute symptoms, we expect that neurological sequelae would be common.

Caveats:

- **No human data on long-term symptoms of cyanogen chloride.**
- **Animal data were only collected for, at most, 25 days after exposure.**
- **No animals were treated or given supportive care.**
- **Many of the conclusions are extrapolated from parallels to hydrogen cyanide.**

H. Hydrogen Sulfide (H_2S)

Hydrogen sulfide is a colorless gas that smells like rotten eggs and can arrest cellular metabolism, just like hydrogen cyanide.[221] Because its mechanism of action is similar to hydrogen cyanide, the symptoms are basically identical, except that hydrogen sulfide also has irritating properties. Acute symptoms include loss of consciousness, dizziness, dyspnea, nausea, vomiting, convulsions, and coma—depending on dose. Although many recover completely from hydrogen sulfide poisoning with no sequelae, some experience chronic neurological defects after hydrogen sulfide exposure. These defects are thought to occur because hydrogen sulfide affects the availability of oxygen in the brain and can lead to brain damage.[222] Many reports have found long-term neurologic sequelae following exposure to hydrogen sulfide. Most of these reports are from industrial or agricultural accidents, and most information was from single case reports or case reports that included only a few people. One difficulty with using this accidental exposure data is that many individuals may have been exposed to multiple toxins at once (especially those exposed to

[221] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 13-2, 13-12.

[222] Milby and Baselt, "Hydrogen Sulfide Poisoning: Clarification," 193.

"sewer gas"). When the effects were reported to be from hydrogen sulfide in the paper, rather than a collection of agents, we assumed they were from only that chemical, although that assumption may bias the results. In addition, treatment was not included as a factor, since all patients received supportive care and science has still not determined how much of a benefit nitrates, hyperbaric oxygen, or other treatment has on hydrogen sulfide symptoms.[223]

All of the reports discussing long-term sequelae (or lack thereof) of acute hydrogen sulfide exposure have been assembled in Table 5 to show the potential rate of occurrence and symptoms of neurological sequelae. In addition, the severity of initial symptoms—defined by the severity levels used in *AMedP-7.5*[224]—are included. If anyone was placed on artificial respiration, he or she was designated as Severity 4, and, if unconsciousness for longer than a few minutes followed by survival without artificial respiration, he or she was designated as Severity 3.

Table 5. Outcomes of Cases of Hydrogen Sulfide Exposure

Patient #	Exposure or Acute Effects Info	Outcome	Severity of Sequelae	Source
1	Sewer gas, Severity 4	1 month: exaggeration of reflexes, tremor, and impaired muscle movement; 3 months: walking normally but chest pain on exertion, neurology unchanged	Severe	Hurwitz and Taylor (1954)[225]
2	H_2S spill, Severity 4	Several months: mild depression and lassitude; 1 year: memory defect for day of accident	Moderate	Kemper (1966)[226]
3	Na_2S spill, Severity 3	2 months: occasional headaches; otherwise, normal	Mild	Stine, Slosberg, and Beacham (1976)[227]

[223] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 13-12–13-14.

[224] Ibid, 2-7–2-9.

[225] L. J. Hurwitz and Gweneth I. Taylor, "Poisoning by Sewer Gas with Unusual Sequelae," *The Lancet* 266, no. 6822 (May 29, 1954): 1110–1112.

[226] F. Dean Kemper, "A Near-Fatal Case of Hydrogen Sulfide Poisoning," *Canadian Medical Association Journal* 94, no. 21 (May 21, 1966): 1130–1131, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1935469/.

[227] Robert J. Stine, Bernard Slosberg, and Bruce E. Beacham, "Hydrogen Sulfide Intoxication: A Case Report and Discussion of Treatment," *Annals of Internal Medicine* 85, no. 6 (1976): 756–758, doi:10.7326/0003-4819-85-6-756.

Patient #	Exposure or Acute Effects Info	Outcome	Severity of Sequelae	Source
4	H_2S fumes, Severity 3	No sequelae	–	Ravizza et al. (1982)[228]
5	Farm H_2S expo–sure, Severity 4	1.5 months: fully recovered but after had slight, persis-tent dizziness	Mild	Kaipainen (1955)[229]
6	H_2S can, Severity 4	No sequelae	–	Milby (1962)[230]
7	H_2S can, Severity 4	No sequelae	–	Milby (1962)
8	H_2S gas leak, Severity 3	Time unclear: mild leg weakness and intermittent headaches	Mild	Whitcraft, Bailey, and Hart (1985)[231]
9	H_2S gas leak, Severity 2	No sequelae	–	Whitcraft, Bailey, and Hart (1985)
10	H_2S gas leak, Severity 2	No sequelae	–	Whitcraft, Bailey, and Hart (1985)
11	H_2S gas leak, Severity 2	No sequelae	–	Whitcraft, Bailey, and Hart (1985)
12	H_2S gas leak, Severity 2	No sequelae	–	Whitcraft, Bailey, and Hart (1985)
13	Roofing asphalt fumes, Severity 4	14 months: continued chronic vegetative state	Severe	Hoidal et al. (1986)[232]
14	Roofing asphalt fumes, Severity 4	No sequelae at 3 months	–	Hoidal et al. (1986)

[228] A. G. Ravizza et al., "The Treatment of Hydrogen Sulfide Intoxication: Oxygen versus Nitrites," *Veterinary and Human Toxicology* 24, no. 4 (August 1982): 241–242, https://www.ncbi.nlm.nih.gov/pubmed/7051515.

[229] W. J. Kaipainen, "Hydrogen Sulfide Intoxication: Rapidly Transient Changes in the Electrocardiogram Suggestive of Myocardial Infarction," *Annales Medicinae Internae Fenniaea* 43 (1954): 97–101 (described in U.S. Environmental Protection Agency, *Hydrogen Sulfide*, EPA-600/1-78-018 (Research Triangle Park, NC: Health Effects Research Laboratory, Office of Research and Development, February 1978), 6-11, https://nepis.epa.gov/Exe/ZyPDF.cgi?Dockey=9100B2YD.PDF).

[230] Thomas H. Milby, "Hydrogen Sulfide Intoxication: Review of the Literature and Report of Unusual Accident Resulting in Two Cases of Nonfatal Poisoning," *Journal of Occupational Medicine* 4, no. 8 (August 1962): 431–437, http://journals.lww.com/joem/Citation/1962/08000/Hydrogen_Sulfide_Intoxication__Review_of_the.7.aspx.

[231] Daniel D. Whitcraft, Todd D. Bailey, and George B. Hart, "Hydrogen Sulfide Poisoning Treated with Hyperbaric Oxygen," *The Journal of Emergency Medicine* 3, no. 1 (1985): 23–25, http://www.jem-journal.com/article/0736-4679(85)90215-X/fulltext.

[232] Charles R. Hoidal et al., "Hydrogen Sulfide Poisoning from Toxic Inhalations of Roofing Asphalt Fumes," *Annals of Emergency Medicine* 15, no. 7 (July 1986): 826–830, https://doi.org/10.1016/S0196-0644(86)80383-3.

Patient #	Exposure or Acute Effects Info	Outcome	Severity of Sequelae	Source
15	Reservoir fumes, Severity 4	No sequelae at 2 years	–	Deng and Chang (1987)[233]
16	Reservoir fumes, Severity 4	No sequelae at 2 years	–	Deng and Chang (1987)
17	Reservoir fumes, Severity 4	No sequelae at 2 years	–	Deng and Chang (1987)
18	Reservoir fumes, Severity 4	No sequelae at 2 years	–	Deng and Chang (1987)
19	H_2S fumes, Severity 4	No sequelae	–	Hsu, Li, and Lin (1987)[234]
20	H_2S fumes, Severity 3	No sequelae	–	Hsu, Li, and Lin (1987)
21	H_2S fumes, Severity 3	No sequelae	–	Hsu, Li, and Lin (1987)
22	H_2S fumes, Severity 3	No sequelae	–	Hsu, Li, and Lin (1987)
23	H_2S fumes, Severity 3	No sequelae	–	Hsu, Li, and Lin (1987)
24	H_2S fumes, Severity 1	5 months: difficulty breathing upon exertion, smoker	Mild	Parra et al. (1991)[235]
25–34	H_2S fumes, Severity 1	No sequelae	–	Parra et al.(1991)
35	H_2S fumes, Severity 2	10 months: quickly became tired, trembling, less initiative, no sense of smell; 2 years: CT and EEG normal; 3 years: sense of smell returned; 5 years: symptoms improved	Severe	Tvedt et al. (1991)[236]

[233] Jou-Fang Deng and Shi-Chuan Chang, "Hydrogen Sulfide Poisonings in Hot-Spring Reservoir Cleaning: Two Case Reports," *American Journal of Industrial Medicine* 11, no. 4 (1987): 447–451, http://onlinelibrary.wiley.com/doi/10.1002/ajim.4700110407/pdf.

[234] P. Hsu, H.-W. Li, and Y. T. Lin, "Acute Hydrogen Sulfide Poisoning Treated with Hyperbaric Oxygen," *Journal of Hyperbaric Medicine* 2, no. 4 (1987): 215–221, http://archive.rubicon-foundation.org/xmlui/bitstream/handle/123456789/4354/JHM_V2N4_5.pdf?sequence=1.

[235] Olga Parra et al., "Inhalation of Hydrogen Sulfide: A Case of Subacute Manifestations and Long Term Sequelae," *British Journal of Industrial Medicine* 48, no. 4 (April 1991): 286–287, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1035373/.

[236] Bjørn Tvedt et al., "Brain Damage Caused by Hydrogen Sulfide: A Follow-Up Study of Six Patients," *American Journal of Industrial Medicine* 20, no. 1 (1991): 91–101, https://pdfs.semanticscholar.org/4521/4a148cde94a17df715d9416d1ed524f3760e.pdf.

Patient #	Exposure or Acute Effects Info	Outcome	Severity of Sequelae	Source
36	Swine manure, Severity 4	3 months: repeatedly said a few words, phrases and names, likely blind, bed-ridden, seizures, incontinence; 8 years later: died	Severe	Tvedt et al. (1991)
37	Hold of spoiled fish, Severity 3	1 week–7 years: reduced sensibility, slight tremor, reduced learning and retention, brain damage	Severe	Tvedt et al. (1991)
38	Hold of spoiled fish, Severity 3	4.5 and 6 years: memory and vision impaired, slower and more rigid movements	Severe	Tvedt et al. (1991)
39	Waste tank, Severity 3	3 months: EEG had slow activity; 8 years: persistent headache, decreased short-term memory; 10 years: generally reduced function, especially visual abilities	Severe	Tvedt et al. (1991)
40	Fetid water, Severity 4	2 months: narrowed vision fields, some hearing loss; 4.5 months: hearing improved, tremor, slightly reduced memory; 5 years: no improvement	Severe	Tvedt et al. (1991)
42	H_2S fumes, Severity 2	9 months: headache, slurred speech, staggering, imbalance, and disorientation	Severe	Callender et al. (1993)[237]
43	H_2S fumes in oil tank, Severity 2	39 months: physical exam normal, but visual recall and reaction time impaired, cognitive functions impaired, and poor balance; 49 months: recall and cognitive speeds improved but reaction time, balance, and color vision had not	Severe	Kilburn (1993)[238]

[237] Thomas J. Callender et al., "Three-Dimensional Brain Metabolic Imaging in Patients with Toxic Encephalopathy," *Environmental Research* 60, no. 2 (February 1993): 295–319, https://doi.org/10.1006/enrs.1993.1039.

[238] Kaye H. Kilburn, "Case Report: Profound Neurobehavioral Deficits in an Oil Field Worker Overcome by Hydrogen Sulfide," *The American Journal of the Medical Sciences* 306, no. 5 (November 1993): 301–305, https://doi.org/10.1097/00000441-199311000-00005.

Patient #	Exposure or Acute Effects Info	Outcome	Severity of Sequelae	Source
44	H_2S fumes, Severity 4	16 days–18 months: slow speech, easily distracted, isolated amnesia, decreased ability to communicate, impaired visual memory, and poor retention of new information	Severe	Snyder et al. (1995)[239]
45	H_2S fumes, Severity 4	No sequelae at 1 year afterwards	–	Snyder et al. (1995)
46	H_2S fumes, Severity 3	No sequelae	–	Snyder et al. (1995)
47	H_2S fumes, Severity 2	No sequelae	–	Snyder et al. (1995)
48	H_2S fumes, Severity 2	No sequelae	–	Snyder et al. (1995)
49	Sewer fumes, Severity 4	3 years: brain deformities, reduced sense of smell, deficits in memory and executive functioning, tremor, and lack of initiative	Severe	Schneider et al. (1998)[240]
50	H_2S from gilsonite mine, Severity 2	1 week–4 years: difficulty breathing upon exertion, smoker	Mild	Duong, Suruda, and Maier (2001)[241]
51	H_2S spill, Severity 2	1 year: slight lightheadedness	Mild	Hirsch (2002)[242]
52	H_2S spill, Severity 2	1 year: slight trouble hearing, trouble with memory and concentration, depression	Mild	Hirsch (2002)
53	H_2S spill, Severity 2	1 year: slight defect in memory and judgment, headache, trouble with vision	Mild	Hirsch (2002)

[239] Jack W. Snyder et al., "Occupational Fatality and Persistent Neurological Sequelae after Mass Exposure to Hydrogen Sulfide," *The American Journal of Emergency Medicine* 13, no. 2 (March 1995): 199–203, https://doi.org/10.1016/0735-6757(95)90094-2.

[240] J. S. Schneider et al., "Persistent Cognitive and Motor Deficits Following Acute Hydrogen Sulfide Poisoning," *Occupational Medicine* 48, no. 4 (May 1998): 255–260, https://www.ncbi.nlm.nih.gov/pubmed/9800424.

[241] Thanh X. Duong, Anthony J. Suruda, and Lisa A. Maier, "Interstitial Fibrosis Following Hydrogen Sulfide Exposure," *American Journal of Industrial Medicine* 40, no. 2 (August 2001): 221–224, http://onlinelibrary.wiley.com/doi/10.1002/ajim.1091/abstract.

[242] Alan R. Hirsch, "Hydrogen Sulfide Exposure without Loss of Consciousness: Chronic Effects in Four Cases," *Toxicology and Industrial Health* 18, no. 2 (March 2002): 51–61, https://www.ncbi.nlm.nih.gov/pubmed/12868793.

Patient #	Exposure or Acute Effects Info	Outcome	Severity of Sequelae	Source
54	H_2S spill, Severity 2	1 year: slight defect in attention, depression, headache, limb weakness	Mild	Hirsch (2002)
55	H_2S fumes, Severity 4	1.5 months: diminished attention, anxious/ depressive, became better after 5 months	Moderate	Nam (2004)[243]
56	Manure tank, Severity 4	2 months: short-term memory problems	Severe	Belley et al. (2005)[244]
57	Manure tank, Severity 4	2 months: no sequelae	–	Belley et al. (2005)
58	Manure tank, Severity 3	No sequelae	–	Belley et al. (2005)
59	Manure tank, Severity 3	No sequelae	–	Belley et al. (2005)
60	Manure tank, Severity 3	No sequelae	–	Belley et al. (2005)
61	Manure tank, Severity 2	No sequelae	–	Belley et al. (2005)
62	Tank of rotten eggs, Severity 4	2 months: balance problems, slowly regaining speech, learning to eat	Severe	Gerasimon et al. (2007)[245]

In total, 62 case reports were found that detailed long-term effects (or lack thereof) from hydrogen sulfide. As with hydrogen cyanide (Section 3.F), the most severe long-term effects often arose after the most severe acute symptoms. These very severe long-term effects, including coma, are likely from brain damage since hydrogen sulfide affects the availability of oxygen in the brain.[246] When looking at the 62 cases, 26 cases had acute symptoms of Severity 1 or 2, 15 cases had acute symptoms of Severity 3, and 21 cases had acute symptoms of Severity 4.

[243] Byungkuk Nam et al., "Neurologic Sequela of Hydrogen Sulfide Poisoning," *Industrial Health* 42, no. 1 (2004): 83–87, https://doi.org/10.2486/indhealth.42.83.

[244] Richard Belley et al., ""Hyperbaric Oxygen Therapy in the Management of Two Cases of Hydrogen Sulfide Toxicity from Liquid Manure," *Canadian Journal of Emergency Medicine* 7, no. 4 (July 2005): 257–261, https://pdfs.semanticscholar.org/37c8/76800f8f1a9f2a037e853e53a29ac273176d.pdf.

[245] Gregg Gerasimon et al., "Acute Hydrogen Sulfide Poisoning in a Dairy Farmer," *Clinical Toxicology* 45, no. 4 (May 2007): 420–423, https://doi.org/10.1080/15563650601180l0.

[246] Milby and Baselt, "Hydrogen Sulfide Poisoning: Clarification."

Of the 26 with mild or moderate acute symptoms (Severity 1 or 2), only 9 had sequelae (34.6%). Many of these sequelae were minor. The four patients described by Hirsch[247] had slight deficits in memory and cognitive function after their hydrogen sulfide exposure, but the individuals were also seeking a lawsuit against the company that spilled the hydrogen sulfide, so their claims may have been biased. In addition, few indications were given that these individuals were significantly impaired by their symptoms. Two smokers reported difficulty breathing upon exertion. The last three patients had much more severe long-term symptoms. One individual lost his sense of smell for 3 years and had difficulties with tiredness, trembling, and lack of motivation for 5 years after hydrogen sulfide exposure.[248] Another individual still had a headache, slurred speech, and imbalance/ disorientation 9 months after hydrogen sulfide exposure.[249] The last individual had moderate acute symptoms from hydrogen sulfide fumes in an oil tank.[250] At 39 months after exposure, he still had impaired visual recall and reaction time, impaired cognitive function, and poor balance. At 49 months after exposure, his cognitive functions had improved, but he still had poor balance and reaction time. These case reports indicate that although most of the long-term effects from mild or moderate hydrogen sulfide exposure were mild (or nonexistent), some had chronic debilitating effects even from a somewhat low dose.

Of the 15 individuals with severe acute symptoms (Severity 3), five had sequelae (33.3%). Of those five individuals, two had mild symptoms mostly restricted to intermittent headaches.[251] Three individuals had more severe long-term symptoms, and all symptoms were described by Tvedt et al.[252] One patient had hyperthyroidism and atrial fibrillation at 2 years and reduced sensitivity in his hands and feet at 4 years after his accident. Neuropsychological exams at 4 and 7 years after the accident indicated that he had reduced learning and memory retention and reduced motor function not explained by age alone. Another patient was evaluated 4.5 years after his accident and had impaired memory and vision as well as reduced motor function. His symptoms remained the same 6 years after the accident. The last patient had a persistent headache and slight short-term memory problems when evaluated 8 years after his accident. The ratios of no, mild, and moderate/ severe sequelae are similar to those observed for individuals with initial mild or moderate symptoms.

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[247] Hirsch, "Hydrogen Sulfide Exposure without Loss of Consciousness."

[248] Tvedt et al., "Brain Damage Caused by Hydrogen Sulfide."

[249] Callender et al., "Three-Dimensional Brain Metabolic Imaging."

[250] Kilburn, "Case Report: Profound Neurobehavioral Deficits in an Oil Field Worker."

[251] Stine, Slosberg, and Beacham, "Hydrogen Sulfide Intoxication: A Case Report"; Whitcraft, Bailey, and Hart, "Hydrogen Sulfide Poisoning Treated with Hyperbaric Oxygen."

[252] Tvedt et al., "Brain Damage Caused by Hydrogen Sulfide."

Of the 21 individuals with very severe acute symptoms (Severity 4), 11 had sequelae (52.4%). Most of these sequelae were moderate or severe. Only one individual had the mild symptom of slight persistent dizziness.[253] The rest had symptoms consistent with moderate or severe brain damage, including memory problems, depression, diminished attention and initiative, visual, hearing, or olfactory deficits, and/or coma. These conditions would likely have a significant effect on the families or caregivers of these individuals and on the medical system. The proportion of severe long-term effects among those individuals with very severe acute symptoms was higher than the proportion for those individuals with mild, moderate, or severe acute symptoms.

Summary reports from large-scale accidents often have very low proportions of individuals with long-term effects but also rarely include information on the initial dose.[254] This lack of information limits their utility in this paper, but these large-scale reports are often cited in other literature as a sign that sequelae from hydrogen sequelae are uncommon. Ahlborg[255] stated that of 58 workers who became unconscious from hydrogen sulfide poisoning, 15 suffered sequelae (25.9%). The workers were not separated out in the analysis, however, and many had a history of repeated poisoning. In addition, the period of recovery was approximately 1.5 months, which is within the criteria for "acute symptoms" in this paper, rather than chronic. Therefore, these 58 workers were not included in Table 5. Chronic symptoms included fatigue, dizziness, poor memory, irritability, and disturbance of equilibrium.[256] Burnett et al.[257] stated that of 221 total cases of hydrogen sulfide poisoning (74% of whom lost consciousness), no long-term sequelae were reported. However, they also said that no follow-up tracings were available after hospital discharge, so it is unclear whether no sequelae were actually in the population or just none were reported. McCabe and Clayton[258] stated that no respiratory or digestive sequelae were reported among 320 people hospitalized after a hydrogen sulfide leak in Mexico but that four people did have neurologic sequelae. Two had neuritis of the acoustic nerve, one had dysarthria, and one had an aggravation of his preexisting epilepsy. They focused on the 47 people who

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[253] Kaipainen, "Hydrogen Sulfide Intoxication. Rapidly Transient Changes" (described in U.S. Environmental Protection Agency, *Hydrogen Sulfide*, 6-11).

[254] Milby and Baselt, "Hydrogen Sulfide Poisoning: Clarification"; W. W. Burnett et al., "Hydrogen Sulfide Poisoning: Review of 5 Years' Experience," *Canadian Medical Association Journal* 117, no. 11 (December 3, 1977): 1277–1281, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1880350/.

[255] G. Ahlborg, "Hydrogen Sulfide Poisoning in Shale Oil Industry," *Archives of Industrial Hygiene and Occupational Medicine* 3, no. 3 (March 1951): 247–266.

[256] Ibid.

[257] Burnett et al., "Hydrogen Sulfide Poisoning: Review of 5 Years' Experience."

[258] L.C. McCabe and G. D. Clayton, "Air Pollution by Hydrogen Sulfide in Poza Rica, Mexico: An Evaluation of the Incident of Nov. 24, 1950," *Archives of Industrial Hygiene and Occupational Medicine* 6, no. 3 (September 1952): 199–213 (described in U.S. Environmental Protection Agency, *Hydrogen Sulfide*, 6-20–6-21).

had more severe acute symptoms, but they did not define how severe those original symptoms were. Kleinfeld et al.[259] also reported no sequelae among 10 victims of hydrogen sulfide, although the victims were exposed for only a short time and no severity of initial symptoms was given.

Because of the disparity in proportions of long-term effects presented between the case studies in Table 5 and in larger scale reviews, no exact proportion of long-term effects is presented in this paper. However, we would anticipate some (<50%) long-term symptoms following exposures in all severity categories except mild acute symptoms, for which few case reports were found. Although no long-term symptoms were found following mild or moderate acute symptoms of hydrogen cyanide, mild or moderate symptoms from hydrogen sulfide could produce severe symptoms. Long-term symptoms severity was still tied to acute exposure, however, since only about a third of the long-term symptoms observed for those individuals with moderate or severe acute symptoms were severe (~33%), but most of the long-term symptoms observed for those individuals with very severe acute symptoms (coma, memory problems, balance problems) were severe (90.9%). Some of the mild symptoms included occasional headache or difficulty breathing upon exertion (found only in two smokers). Since no information was found on untreated patients, no conclusions could be made about long-term effects following untreated exposure to hydrogen sulfide.

No more papers were found describing long-term effects of hydrogen sulfide. Therefore, further literature analysis is not recommended at this time. This recommendation may be revisited in a few years if interest in potential long-term effects of hydrogen sulfide injury continues and new papers related to the topic are published.

[259] M. Kleinfeld, C. Giel, and A. Rosso, "Acute Hydrogen Sulfide Intoxication: An Unusual Source of Exposure," *Indian Medicine and Surgery* 33, no. 9 (1964): 656–660 (described in U.S. Environmental Protection Agency, *Hydrogen Sulfide*, 6-16–6-17).

Conclusion: No reports were found on untreated exposures to hydrogen sulfide. Long-term symptoms of hydrogen sulfide exposure were similar to those from hydrogen cyanide. These symptoms included headache, memory problems, deficits in vision, hearing, or smell, and coma. Although some patients slowly recovered from their symptoms over years, others never did. Mild long-term effects (headache, slight balance problems) were more common in those patients with moderate or severe acute symptoms, while severe long-term effects (coma, memory/mood problems, loss of senses) were more common in those patients with very severe acute symptoms. Severe effects accounted for 90% of long-term effects following very severe acute symptoms but only 33% of long-term effects following moderate or severe acute symptoms. Although 33%–55% of the case reports that included follow-up had long-term symptoms, review articles and exposures involving more people indicated that the percentage was much lower. These review articles and descriptions of larger exposures, however, often did not include acute symptom severity or did not say whether or how they followed up with these patients, so they could not be used in our analysis.

Caveats:

- **Sixty two case reports were found describing chronic effects of hydrogen sulfide exposure.**
- **Some case reports described inhalation of "sewer fumes" or other mixtures, so the effects of hydrogen sulfide may have been conflated with those of other agents.**
- **All patients were treated.**
- **Significant sequelae may be overrepresented in the literature, and the proportion of long-term effects varies greatly between reports from large accidents and analysis of case reports in the literature.**

I. Conclusions

Several chemical agents discussed in *AMedP-7.5*[260] can lead to significant long-term complications, although the severity of those complications varies by illness and initial dose. This analysis determines the feasibility of describing CBRN effects that occur well after the initial exposure. Therefore, not only does this analysis briefly describe the long-term effects of each agent, it also indicates how much more information is available and which agents to prioritize if further study is done in the future.

The chemical agents are divided into three groups for how much more information would potentially be available: no data, little data, or more data (see Table 6). These are the same categories as used for biological data in Table 2. All of the chemical agents had at least some data available, although most fell into the "little data" category.

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

Table 6. Amount of Data Found for Chemical Agents

No Data	Little Data	More Data
	Phosgene	Nerve agents
	Ammonia	Sulfur mustard
	Hydrogen cyanide	Chlorine
	Cyanogen chloride	
	Hydrogen sulfide	

The chemical agents, all of which had at least some long-term effect, were further categorized by the type of long-term effects observed (see Table 7). The categorization was done differently than that for the biological agents. One reason was that since many of the long-term effects of chemical agents are tied to initial dose and acute symptoms, the dose-response of the sequelae was categorized as "no dose effect/none recorded," "some dose effect," or "only in severe." In addition, agents were split up by the body system that was affected (nervous, respiratory, dermatological, and visual). No percentages were included for rate of effect, since many effects were dose-dependent or the rate could not be determined.

Table 7. Effects of Treated Chemical Agents

Dose Effect	Neurological	Respiratory	Ocular	Dermatological
No Dose Effect/ None Reported		CG		
Some Dose Effect	Nerve H_2S	HD Cl_2	HD	HD
Only in Severe	AC CK	NH_3	NH_3	

Note: AC = hydrogen cyanide, CG = phosgene, CK = cyanogen chloride, Cl_2 = chlorine, H_2S = hydrogen sulfide, HD = sulfur mustard, NH_3 = ammonia.

Dose-dependence was a key feature of the long-term effects of many agents. Some agents, such as hydrogen cyanide, only produce long-term effects in people with severe or very severe acute symptoms, as a secondary result of an acute symptom (e.g., acute brain hypoxia causing brain damage that leads to long-term effects). Those individuals with mild or moderate symptoms recover fully. Acute symptom severity was used as a proxy for dose since the exact agent dose was not known for almost any of the reports. Three categories were used for dose dependence. The first was "no dose effect/none recorded" for agents that did not appear to have sequelae related to initial dosage or so few cases that a dosage response could not be determined. The only agent in this category was phosgene, for which sequelae are very rare and more related to smoking status than initial dose. The second was "some dose effect." For these agents, sequelae can arise after mild or moderate acute doses,

but sequelae are generally milder or rarer after lower doses than higher ones. Four agents fell into this category: nerve agents, sulfur mustard, chlorine, and hydrogen sulfide. The final category was "only in severe." For these agents, sequelae arose only in those with severe or very severe acute symptoms. Three agents fell into this category: ammonia, hydrogen cyanide, and cyanogen chloride. In addition to dose, other factors may also influence whether someone develops sequelae, such as smoking status for phosgene, chlorine, and ammonia.

All of the agents produced long-term symptoms localized to specific organ systems. The most common organ systems affected were the neurological and respiratory systems. Neurological sequelae generally included sleep disorders, personality changes, irritability, memory problems, and sometimes coma. Many of these symptoms can cause massive declines in quality of life for the individual and for any caregiver. Most of the agents that produce neurological sequelae only cause severe sequelae after large initial doses (severe or very severe acute symptoms). These agents include nerve agents, hydrogen cyanide, cyanogen chloride, and hydrogen sulfide. Respiratory sequelae included chronic bronchitis, cough, and difficulty breathing (either constitutively or upon exertion). Sometimes, these sequelae can be more prevalent in smokers. Respiratory sequelae are sometimes tied to dose but are generally more likely to occur with mild or moderate acute doses than neurological sequelae. Agents that produce respiratory sequelae include sulfur mustard, phosgene, chlorine, and ammonia. Ocular sequelae include corneal scratches, decreases in vision, and sometimes blindness and can occur after sulfur mustard injury or splashes of ammonia into the eye but are much rarer than other sequelae. Dermatological sequelae can occur after sulfur mustard injury and include scarring, hyper/hypopigmentation, skin lesions, itching, and dry skin. Most of these effects are mild; however, depending on the location of injury, the effects may cause significant discomfort.

Most of the individuals exposed to chemical agents in the literature were treated. Therefore, no information on long-term effects was available on an untreated population. Many people were treated only with supportive care, except those exposed to agents for which a specific treatment is available (those people generally were treated with both).

4. Conclusions and Recommendations

A. Summary

In total, 27 agents (15 biological and 12 chemical) were studied for potential long-term effects from acute exposure. Since this is a quick-look analysis, 21 of the agents were investigated fully in this paper, while 6 agents were summarized only briefly and are recommended for further analysis (see Section 4.B). All but two agents (ricin and T-2) had some information on long-term sequelae, and all but four (ricin, T-2, plague, and SEB) had some long-term sequelae associated with the illness or agent. These sequelae range from mild to severe and can be common or incredibly uncommon. Although mild sequelae, such as occasional headaches, may not affect an individual's ability to perform tasks, other problems such as difficulty breathing or a relapse of symptoms can affect that ability. Many of the severe long-term effects that can result from chemical or biological agents, such as personality changes, memory problems, or blindness, would not only affect the individual's ability to perform required tasks, but also likely affect the rest of his or her life and potentially even his or her caregiver's life. Additional medical resources, such as additional antibiotics, may be required for certain long-term effects. 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/illness.

The long-term effects found from biological agents can be split into five categories: no effect, mild effect, relapse, severe effect, or not applicable (N/A). The relative percentage of people expected to show the effect was also categorized into <3%, ~3%–50%, or >50%. The percentages are not exact and just work as general guidelines. Sequelae may be overrepresented in the literature since those individuals who did not have long-term effects often do not follow up with a doctor. Some agents, such as treated anthrax, also had percentages based on fewer than 10 people.

"Mild effect" was defined as an effect such as slight hand tremor, which would not have a significant effect on the person's life or an effect that lasted less than 1 year and was not debilitating. The three agents that produced mild effects were Q fever (chronic fatigue syndrome), VEE (slight hand tremor or insomnia), and untreated tularemia (acute symptoms could last up to 15 months). "Relapse" was defined as an illness with periods of remission and reappearance of the same symptoms, usually with the same severity, either in untreated or treated cases (even with proper use of antibiotics). Untreated and treated brucellosis, glanders, and melioidosis all had moderate (3%–50%) rates of relapse, with

symptoms similar to 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 quality of life or health resources. Five agents produced severe effects at least some of the time. Smallpox caused blindness in less than 1% of cases in one report, and Q fever causes endocarditis in less than 1% of people, especially those with previous valvular defects. EEE, when it manifests as encephalitis, can produce moderate (3%–50%) rates of long-term neurological sequelae, including intellectual disability and the inability to speak or self-feed. Anthrax can produce significant respiratory difficulties in most people (>50%), and botulism can produce weakness, exercise intolerance, and difficulty breathing, speaking, or swallowing in most people (>50%), especially those with severe acute symptoms. Not applicable ("N/A") was defined as illnesses for which no data were available on chronic effect (ricin, T-2 mycotoxin) or illnesses with a ~100% lethality (untreated anthrax and plague). Some of these categories are subjective. Effects that were self-reported or may have a significant psychological component, such as chronic fatigue, are especially difficult to categorize. The biological agents are categorized in Table 8.

Table 8. Effects of Biological Agents

Percent of Population with Long-Term Effect	No Effect	Mild Effect	Relapse	Severe Effect	N/A
<3% of cases				Smallpox	
				Q Fever (Un and Tr)	
~3%–50% of cases		Q Fever (Un and Tr)	Brucellosis (Un and Tr)	EEE	
		VEE	Glanders (Un and Tr)		
		WEE	Melioidosis (Un and Tr)		
		Tularemia (Un)			
>50% of cases	Plague (Tr)			Anthrax (Tr)	Anthrax (Un)
	SEB			Botulism (Un and Tr)	Plague (Un)
	Tularemia (Tr)				Ricin
					T-2

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

The long-term effects of chemical agents, in contrast to those of biological agents, were split up by the body system affected (neurological, respiratory, ocular, and dermatological) and by the dose-response of the sequelae. All victims were either treated with supportive care or, when applicable, specific treatments such as atropine, so no conclusions could be drawn about untreated exposures.

All of the agents produced long-term symptoms localized to specific organ systems. The most common organ systems affected were the neurological and respiratory systems. Nerve agents, hydrogen cyanide, cyanogen chloride, and hydrogen sulfide can produce neurological sequelae, but most only produced severe sequelae after large initial doses (severe or very severe acute symptoms). Neurological sequelae include sleep disorders, personality changes, irritability, memory problems, and sometimes coma. Many of these symptoms can cause massive declines in quality of life for the individual and for any caregiver. Therefore, individuals with severe or very severe acute symptoms from these agents may need to be especially monitored or may require significant additional care after acute recovery.

Sulfur mustard, phosgene, chlorine, and ammonia can produce respiratory sequelae. Respiratory sequelae include chronic bronchitis, cough, and difficulty breathing (either constitutively or upon exertion). Sometimes, these sequelae can be more prevalent in smokers. Respiratory sequelae are sometimes tied to dose but are generally more likely to occur with mild or moderate acute doses than neurological sequelae.

Ocular sequelae, such as corneal scratches, decreases in vision, and sometimes blindness, can occur occasionally after sulfur mustard injury or splashes of ammonia in the eye. Ocular sequelae are much rarer than other sequelae. Sulfur mustard can produce dermatological sequelae, including scarring, hyper/hypopigmentation, skin lesions, itching, and dry skin. Most of these effects are mild; however, depending on the location of injury, the effects may cause significant discomfort.

Dose dependence was the other key feature of the long-term effects from many agents. Some agents, such as hydrogen cyanide, only produce long-term effects in people with severe or very severe acute symptoms. Those with mild or moderate symptoms recover fully. Because the exact agent dose was not reported in almost any of the reports, acute symptom severity was used as a surrogate for dose. Three categories were used to describe dose dependence. The first was “no dose effect/none recorded” for agents whose sequelae did not appear to be affected by initial dosage or so few cases were recorded that a dosage response could not be determined. The only agent in this category was phosgene, for which sequelae are very rare and more related to smoking status than initial dose. The second was “some dose effect” for agents whose sequelae after mild or moderate acute doses are generally milder or rarer after lower doses than higher ones. Four agents/agent classes fell into this category: nerve agents, sulfur mustard, chlorine, and hydrogen sulfide. The final category was “only in severe,” for agent whose sequelae occurred only in those with severe or

very severe acute symptoms. Three agents fell into this category: ammonia, hydrogen cyanide, and cyanogen chloride. In addition to dose, other factors may also influence whether someone develops sequelae, such as smoking status for phosgene, chlorine, and ammonia. The long-term effects of chemical agents are summarized in Table 9.

Table 9. Effects of Treated Chemical Agents

Dose Effect	Neurological	Respiratory	Ocular	Dermatological
No Dose Effect/ None Reported		CG		
Some Dose Effect	Nerve H_2S	HD Cl_2	HD	HD
Only in Severe	AC CK	NH_3	NH_3	

Note: AC = hydrogen cyanide, CG = phosgene, CK = cyanogen chloride, Cl_2 = chlorine, H_2S = hydrogen sulfide, HD = sulfur mustard, NH_3 = ammonia.

B. Recommendations

This paper is a quick-look analysis of the long-term effects from the chemical and biological agents described in *AMedP-7.5*.[261] Of the 23 agents/agent classes described in *AMedP-7.5*, all but 4 had at least one report of long-term symptoms following exposure. Two of those four had no information on potential long-term effects, and the other two had some follow-up of individuals who had recovered (they all recovered fully). Seventeen total agents had a small enough dataset on long-term effects in the literature that they could be fully described in this paper. Only six agents or agent classes—nerve agents, sulfur mustard, chlorine, Q fever, brucellosis, and melioidosis—are recommended for further study.

Table 10 provides the list of all agents separated by amount of information available on long-term effects. With further study of these six agents/classes, a full conclusion could be made for the long-term effects of all agents in *AMedP-7.5*, at least as far as the literature that is available. This analysis may need to be revisited in a few years, especially for those agents with very little information on long-term effects, to see if more information is then found in the literature.

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

Table 10. 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	
	SEB	
	Phosgene	
	Ammonia	
	Hydrogen cyanide	
	Cyanogen chloride	
	Hydrogen sulfide	

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Appendix A.
Illustrations

Tables

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Appendix B.
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Appendix C.
Abbreviations

AC	hydrogen cyanide
AMedP	Allied Medical Publication
ATP	adenosine triphosphate
C≡N	cyanide moiety
CBRN	chemical, biological, radiological, and nuclear
CG	phosgene
CK	cyanogen chloride
–Cl	chlorine moiety
Cl	Chlorine
Cl2	chlorine
CN	Cyanide
CT	computed tomography
ECt50-severe	concentration producing severe effects in 50% of the population
EEE	Eastern Equine Encephalitis
EEG	electroencephalogram
GSI	Global Severity Index
H2S	hydrogen sulfide
HCN	hydrogen cyanide
HD	sulfur mustard
HgCN	mercury cyanide
IDA	Institute for Defense Analyses
KCN	potassium cyanide
mg-min/m3	milligram-minutes per cubic meter
N/A	not applicable
Na_2S	sodium sulfide
NaCN	sodium cyanide
NATO	North Atlantic Treaty Organization
NH3	ammonia
OTSG	Office of the Surgeon General
PTSD	post-traumatic stress disorder
RADS	Reactive Airway Dysfunction Syndrome
REM	rapid eye movement
SEB	Staphylococcal enterotoxin B
TIC	toxic industrial chemical
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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14. ABSTRACT

This report is a quick look at the long-term effects which can occur after acute exposure to the 23 chemical and biological agents/agent classes described in *NATO Allied Medical Publication 7.5 (AMedP-7.5)*. All but six of the agents were described fully in this paper and long-term effects ranged from mild to severe and common to very rare. The six agents which had more information than could be summarized in this quick study are recommended for further analysis at a later time.

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