STANDARDS RELATED DOCUMENT

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Technical Reference Manual NATO Planning Guide for the Estimation of CBRN Casualties

Edition A Version 1

JANUARY 2018

NORTH ATLANTIC TREATY ORGANIZATION

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NORTH ATLANTIC TREATY ORGANIZATION (NATO)

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NATO LETTER OF PROMULGATION

17 January 2018

1. The enclosed Standards Related Document, AMedP-7.5-1, Edition A, Version 1, TECHNICAL REFERENCE MANUAL NATO PLANNING GUIDE FOR THE ESTIMATION OF CBRN CASUALTIES, which has been approved in conjunction with AMedP-7.5 publication by the nations in the Military Committee Medical Standardization Board, is promulgated herewith.

2. AMedP-7.5-1, Edition A, Version 1 is effective upon receipt.

4. This publication shall be handled in accordance with C-M(2002)60.

Edvardas MAŽEIKIS
Major General, LTUAF
Director, NATO Standardization Office

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INSTITUTE FOR DEFENSE ANALYSES

Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5) NATO Planning Guide for the Estimation of CBRN Casualties

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About This Publication

This work was conducted by the Institute for Defense Analyses (IDA) under contract HQ0045-14-D-0001, project CA-6-3079, “CBRN Casualty Estimation and Support to the Medical CBRN Defense Planning & Response Project,” for the Joint Staff, Joint Requirements Office (JRO) for Chemical, Biological, Radiological and Nuclear (CBRN) Defense (J-8/JRO) and the US Army Office of The Surgeon General (OTSG). The views, opinions, and findings should not be construed as representing the official position of either the Department of Defense or the sponsoring organization.

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Executive Summary

This is the Technical Reference Manual (TRM) for *Allied Medical Publication 7.5* (*AMedP-7.5*), titled *NATO Planning Guide for the Estimation of CBRN Casualties*. *AMedP-7.5* is the doctrinal replacement for *Allied Medical Publication 8(C)*. Like its predecessor document, *AMedP-7.5* describes a methodology for estimating casualties that uniquely occur as a consequence of chemical, biological, radiological, and nuclear (CBRN) incidents near Allied forces. Improvements relative to *AMedP-8*(*C*) include an expanded list of chemical, biological, and radiological agents and the incorporation of medical treatment into the models for each agent and effect. In addition, to simplify and streamline the document, *AMedP-7.5* includes only the information necessary to understand and implement the methodology. Because *AMedP-7.5* is simplified and streamlined, it does not fully explain *why* the models are what they are. This TRM fills that gap; it:

- Describes the sources for, and justification of, the assumptions, limitations, and constraints and recommended values employed by *AMedP-7.5*;
- Identifies, where appropriate, the sources for definitions and key terms used by *AMedP-7.5*, or else describes where and how new definitions and terms were derived;
- Documents the derivation and/or supporting reasoning for the modeled symptomatology and the associated parameter values, lookup tables, equations, assumptions, limitations, constraints, and injury profiles for each agent or effect included in *AMedP-7.5*; and
- Provides a list of the references used in the development of *AMedP-7.5*.

Note that this TRM assumes familiarity with *AMedP-7.5* and does not reiterate or expand on its description of the casualty estimation methodology. Rather, this document provides information beyond the scope of *AMedP-7.5* that will allow for transparency and verification of the methodology. The goal is to make the data underlying the components of *AMedP-7.5*, and the process through which it was developed, as clear as possible and to enable analysts and modelers to understand and replicate these results and procedures.

Accordingly, we anticipate this document will be a reference for those who actively use *AMedP-7.5*, have a copy of *AMedP-7.5* at hand, and wonder why a certain equation or parameter value is used. We do not anticipate that users will read this entire document; rather, they will simply find the section that gives the answer to the question at hand. If this document does not provide the explanation sought, the likely reason is that we considered the section of *AMedP-7.5* in question to be sufficiently self-explanatory (another possibility is an oversight on our part). If you require additional explanation, please email Dr. Sean Oxford of the Institute for Defense Analyses at soxford@ida.org.

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1.1. Introduction

Introduction

The North Atlantic Treaty Organization (NATO) has produced a series of Allied Medical Publications on chemical, biological, radiological, and nuclear (CBRN) planning and casualty estimation. *Allied Medical Publication 8* (*AMedP-8*) *Nuclear*[1] was published in 2002 as the NATO methodology for estimating nuclear casualties. A few years later, *AMedP-8*(*A*) *Chemical*[2] was published, and it documented estimates of chemical casualties resulting from exposure to the nerve agents sarin (GB), VX, and the blister agent distilled mustard (HD). The publication of *AMedP-8*(*B*) *Biological*[3] followed shortly thereafter. It described the processes for estimating casualties resulting from exposure to biological agents of military concern. In 2011, a new version of *AMedP-8* (*AMedP-8*(*C*), *NATO Planning Guide for the Estimation of CBRN Casualties*)[4] was published, and it standardized the methodology across CBRN agents and effects and allowed users the flexibility to modify specific human response parameters.

The most recent version of the methodology is documented in *Allied Medical Publication 7*.5 (*AMedP-7.5*),[5] an updated and renamed[6] publication of the NATO planning guide. Like its immediate predecessor, *AMedP-7.5* describes a methodology for estimating casualties uniquely occurring as a consequence of CBRN incidents near Allied forces. Improvements relative to *AMedP-8*(*C*) include an expanded list of chemical, biological, and radiological agents and the incorporation of medical treatment into the models for each agent and effect. In addition, to simplify and streamline the document, *AMedP-7.5* includes only the information necessary to understand and implement the methodology.

This Technical Reference Manual (TRM) serves as a supplement to *AMedP-7.5*, documenting the analyses, rationale, and underlying data utilized in the development of the methodology. The TRM assumes familiarity with *AMedP-7.5* and does not reiterate or expand on its description of the casualty estimation methodology. Rather, this document

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1 North Atlantic Treaty Organization (NATO), *AMedP-8*(*A*)*, Volume I: Medical Planning Guide of NBC Battle Casualties* (*Nuclear*), STANAG 2475 (Brussels: NATO, 2002).

2 North Atlantic Treaty Organization (NATO), *AMedP-8*(*A*)*, Volume III: Medical Planning Guide of NBC Battle Casualties* (*Chemical*), STANAG 2477 (Brussels: NATO, 2005).

3 North Atlantic Treaty Organization (NATO), *AMedP-8*(*B*)*, Volume II: Medical Planning Guide of CBRN Battle Casualties* (*Biological*), STANAG 2476 (Brussels: NATO, 2007).

4 North Atlantic Treaty Organization (NATO), *AMedP-8*(*C*)*, NATO Planning Guide for the Estimation of CBRN Casualties*, STANAG 2553 (Brussels: NATO, 2011).

5 North Atlantic Treaty Organization (NATO), *AMedP-7.5: NATO Planning Guide for the Estimation of CBRN Casualties* FINAL DRAFT, STANAG 2553 (Brussels: NATO, study).

6 The change in designation from *AMedP-8*(*C*) to *AMedP-7.5* reflects a change in NATO publication naming conventions, but the title of the document remains the same (*NATO Planning Guide for the Estimation of CBRN Casualties*).

provides information beyond the scope of *AMedP-7.5* that will allow for transparency and verification of the methodology.

Much of the analysis supporting the development of *AMedP-7.5* was previously documented in various reports by the Institute for Defense Analyses (IDA), which serve as the basis for this TRM. The earliest of these source documents is the *AMedP-8*(*C*) TRM,[7] which provides an explanation of the historical development of Injury Profiles for the agents and effects in *AMedP-8*(*C*) and justifies agent-specific parameter values and assumptions. Soon after the *AMedP-8*(*C*) TRM was finished, IDA published a report[8] on the parameter values necessary to model five additional biological agents. The list of agents included in the methodology was further expanded in 2015 with the publication of 2 reports[9] on parameter values for 10 additional chemical agents and 5 biological agents/toxins. Additional IDA reports relevant to the expansion and explanation of the methodology include a 2012 publication[10] on the incorporation of medical treatment and a 2014 comparison of human response parameter values for chemical and biological threat agents included in DOD and NATO doctrine, both of which help justify many of the values incorporated in *AMedP-7.5*.[11] The majority of this TRM is derived from these six IDA documents, with many sections taken verbatim and others modified as necessary for consistency in terminology and style or to reflect any subsequent modifications after publication. Note that some of the IDA documents and certain references cited therein are not releasable to NATO due to U.S. restrictions on the distribution of their contents. The intent of this document, however, is to present the underlying source data on which decisions were based and thereby preclude the need to access any restricted distribution documents directly.

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7 Carl A. Curling et al., *Technical Reference Manual: NATO Planning Guide for the Estimation of Chemical, Biological, Radiological, and Nuclear (CBRN) Casualties, Allied Medical Publication-8(C)*, IDA Document D-4082 (Alexandria, VA: Institute for Defense Analyses, August 2010).

8 Carl A. Curling et al., *Parameters for the Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia*, IDA Document D-4132 (Alexandria, VA: Institute for Defense Analyses, November 2010).

9 Sean M. Oxford et al., *Parameters for Estimation of Casualties from Phosgene, Chlorine, Hydrogen Cyanide, Cyanogen Chloride, Hydrogen Sulfide, B. pseudomallei, Eastern and Western Equine Encephalitis Viruses, Ricin, and T-2 Mycotoxin*, IDA Paper P-5140 (Alexandria, VA: Institute for Defense Analyses, September 2015) FOUO; and Audrey C. Kelley, Parameters for Estimation of Casualties from Ammonia (NH_3), Tabun (GA), Soman (GD), Cyclosarin (GF), and Lewisite (L), IDA Paper P-5158 (Alexandria, VA: Institute for Defense Analyses, October 2015).

10 Carl A. Curling et al., *The Impact of Medical Care on Casualty Estimates from Battlefield Exposure to Chemical, Biological and Radiological Agents and Nuclear Weapon Effects*, IDA Document D-4465 (Alexandria, VA: Institute for Defense Analyses, March 2012).

11 Sean M. Oxford, Audrey C. Kelley, and Carl A. Curling, *Comparison of Chemical and Biological Human Response Parameter Values in NATO and U.S. Doctrine*, IDA Document D-4799 (Alexandria, VA: Institute for Defense Analyses, June 2014) FOUO.

Purpose

As stated in *AMedP-7.5*:[12]

> The purpose of [the document *AMedP-7.5*] is to describe a methodology for estimating casualties uniquely occurring as a consequence of CBRN incidents near Allied forces, in support of the planning processes described in Allied Joint Publication 3.8 (AJP-3.8), *Allied Joint Doctrine for NBC Defence*,[13] Allied Joint Publication 4.10 (AJP-4.10), *Allied Joint Medical Support Doctrine*,[14] Allied Joint Medical Publication 1 (AJMedP-1), *Allied Joint Medical Planning Doctrine*,[15] Allied Joint Medical Publication 7 (AJMedP-7), *Allied Joint Medical Doctrine for Support to CBRN Defensive Operations*,[16] and Allied Medical Publication 7.6 (AMedP-7.6), *Commander's Guide on Medical Support to Chemical, Biological, Radiological, and Nuclear* (*CBRN*) *Defensive Operations*.[17]
>
> The purpose of the methodology is to estimate the number, type, severity, and timing of CBRN casualties.
>
> The purpose of CBRN casualty estimates is to assist planners, logisticians, and other staff officers in quantifying contingency requirements for medical force structure, specialty personnel, medical materiel, and patient transport or evacuation.

The purpose of this TRM is to describe the information presented in or used to develop the methodology described in *AMedP-7.5*. This document will:

- Describe the sources for, and justification of, the assumptions, limitations, and constraints and recommended values employed by the methodology;
- Identify, where appropriate, the sources for definitions and key terms used by the methodology, or else describe where and how new definitions and terms were derived;
- Document the derivation and/or supporting reasoning for the modeled symptomatology and the associated parameter values, lookup tables, equations, assumptions, limitations, constraints, and Injury Profiles for each agent of effect included in the methodology; and

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12 NATO, *AMedP-7.5*, 1-2–1-3.

13 North Atlantic Treaty Organization (NATO), *AJP-3.8*(*A*)*: Allied Joint Doctrine for CBRN Defence*, STANAG 2451 (Brussels: NATO, 30 March 2012).

14 North Atlantic Treaty Organization (NATO), *AJP-4.10*(*A*)*: Allied Joint Medical Support Doctrine*, STANAG 2228 (Brussels: NATO, 3 March 2006).

15 North Atlantic Treaty Organization (NATO), *AJMedP-1: Allied Joint Medical Planning Doctrine*, STANAG 2542 (Brussels: NATO, 3 November 2009).

16 North Atlantic Treaty Organization (NATO), *AJMedP-7: Allied Joint Medical Doctrine for Support to CBRN Defensive Operations*, STANAG 2596 (Brussels: NATO, 25 August 2015).

17 North Atlantic Treaty Organization (NATO), *AMedP-7.6: Commander's Guide on Medical Support to Chemical, Biological, Radiological, and Nuclear (CBRN) Defensive Operations*, STANAG 2873 (Brussels: NATO, study).

- Provide a list of the references used in the development of this methodology and its human response models.

The goal is to make the data underlying the components of the *AMedP-7.5* methodology and the process through which it was developed as clear as possible and to enable analysts and modelers to understand and replicate these results and procedures.

How to Use the Technical Reference Manual

Elements of this TRM will not make sense if the reader is not familiar with, or does not have available for reference, *AMedP-7.5*. In other words, we anticipate this document will be a reference for someone who is actively using *AMedP-7.5*, has a copy of *AMedP-7.5* at hand, and is wondering why a certain equation or parameter is what it is. We do not anticipate that readers will read this entire document; rather, they will simply find the section that gives the answer to the question at hand. If this document does not provide the explanation sought, the likely reason is that we considered the section of *AMedP-7.5* in question to be sufficiently self-explanatory (another possibility is an oversight on our part). If you require additional explanation, please email Dr. Sean Oxford of the Institute for Defense Analyses at soxford@ida.org.

On a separate note, this TRM is not intended to provide advice on any aspect of providing medical care. Accordingly, to the extent possible, we have avoided describing specific antidotes or procedures. However, to justify many model parameters, we often used data from specific cases in which specific medical treatment was provided. Such uses of data do not reflect an endorsement of any particular medical course of action; rather, they reflect the data that were available for constructing models. For medical guidance, see *AMedP-7.1* (tactical level guidance)[18] and *AMedP-7.6* (operational level guidance).[19]

Background

Predecessor Methodologies

Previous versions of the NATO planning guide used existing agent-specific approaches to provide estimates of casualties occurring as a consequence of CBRN attacks against military targets for planning purposes. These approaches all developed user-defined, time-based casualty and fatality estimates based on descriptions of the significant underlying signs and symptoms and their changing severity over time. When applicable, these methodologies helped provide the basis for the *AMedP-7.5* methodology.

The earlier *AMedP-8* nuclear methodology relied on an approach developed as part of the Intermediate Dose Program (IDP) by Pacific Sierra Research Corporation (PSR), under contract to the Defense Nuclear Agency (DNA). This methodology is based on a model developed by PSR that correlates the severity of signs and symptoms resulting from

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18 North Atlantic Treaty Organization (NATO), *AMedP-7.1: Medical Management of CBRN Casualties*, STANAG 2461 (Brussels: NATO, study).

19 NATO, *AMedP-7.6*.

acute radiation doses in six physiological systems to performance and publishes the correlation over time as a set of dose-responses.[20] Subsequently, Technico Southwest, Inc. used the same methodology to develop dose-responses detailing the results of blast and thermal injury. Then, using a team of subject-matter experts (SMEs), Technico Southwest, Inc. used the initial individual insult—radiation, blast, and thermal—dose-responses to generate combined Injury Profiles and the associated combined injury performance values. These performance values are the basis for the *Combined* algorithms,[21] which were then incorporated into the Consolidated Human Response Nuclear Effects Model (CHRNEM) combined injury software tool.[22]

The IDP methodology was modified for use with chemical agents as well and incorporated into the DNA Improved Casualty Estimation (DICE) tool to estimate human performance.[23] The DICE algorithms use the signs and symptoms resulting over time from a single exposure to a chemical insult to determine human performance and were employed in earlier versions of the NATO casualty estimation methodology.

For biological agent human response modeling in early versions of *AMedP-8*, two different methodologies were used to determine the severities associated with each agent exposure. For *Francisella tularensis* (tularemia), staphylococcal enterotoxin B (SEB), and *Coxiella burnetti* (Q fever), PSR used clinical data from military research volunteers who participated in controlled human exposure and medical countermeasure development studies during the 1950s and 1960s. The clinical records provided data that were used to generate time- and dose-dependent febrile models. Performance algorithms based on the febrile models were derived from physical and cognitive test results from the research volunteers.[24]

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20 George H. Anno et al., "Symptomatology of Acute Radiation Effects in Humans After Doses of 0.5 to 30 Gy," *Health Physics* 56, no. 6 (June 1989): 821–38.

21 *Combined* is an executable program that uses a specific set of stand-alone algorithms and references the individual R-B-T and combined performance values to calculate the performance over time resulting from combined R-B-T insults identified as inputs to the program. Although *Combined* can be run independently, it has also been incorporated into the CHRNEM tool.

22 Sheldon G. Levin, *The Effect of Combined Injuries from a Nuclear Detonation on Soldier Performance*, DNA-TR-92-134 (Alexandria, VA: Defense Nuclear Agency, 1993).

23 Arthur P. Deverill and Dennis F. Metz, *Defense Nuclear Agency Improved Casualty Estimation (DICE) Chemical Insult Program Acute Chemical Agent Exposure Effects*, DNS-TR-93-162 (Washington, DC: Defense Nuclear Agency, May 1994).

24 George H. Anno et al., *Consequence Analytic Tools for NBC Operations Volume 1: Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B (SEB) and Q Fever*, DSWA-TR-97-61-V1 (Washington, DC: Defense Special Weapons Agency, October 1998).

The Knowledge Acquisition Matrix Instrument (KAMI)[25] was used to gather information about biological agents for which only limited human response data were available. In 1998, surveys were distributed to SMEs who had experience or knowledge gained from animal studies, accidental exposures, vaccine development, and other sources regarding anthrax, plague, botulism, and Venezuelan equine encephalitis (VEE). Disease models were designed based on SME consensus regarding agent infectivity, lethality, pathology, and times to onset and death or recovery. The KAMI was revised in 1999 to achieve similar consensus about smallpox, brucellosis, and glanders. Illness category tables were generated for each agent, including dose bands and the expected signs and symptoms associated with the given band. Onset times, incidence of infection, and, for some agents, limited symptoms are included in the tables for the KAMI-derived agents.

SME Meetings

In the course of developing *AMedP-8*(*C*) from these existing methodologies, several meetings were held to gather the inputs of recognized SMEs in each subject area.[26] At the chemical, radiological, and nuclear human response meetings, groups of international SMEs discussed and reached concurrence on both the symptom severity level descriptions relevant to each physiological system and the symptom progression maps proposed for use in the *AMedP-8*(*C*) methodology. At the biological human response meeting, after SMEs reviewed and discussed the use of the five submodels to represent the biological agent Injury Profile that provided the basis for the underlying proposed methodology, a consensus approval on the use of these submodels was reached. The details of the four agent-specific meetings, including the dates, locations, and participating SMEs are provided below.

The following SMEs were present at the 21–22 April 2008 chemical human response meeting in Munich, Germany:

- Canada

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25 George H. Anno et al., *Biological Agent Exposure and Casualty Estimation: AMedP-8* (*Biological*) *Methods Report*, GS-35F-4923H (Fairfax, VA: General Dynamics Advanced Information Systems, May 2005).

26 Julia K. Burr et al., *Proceedings of the NATO Chemical Human Response Subject Matter Expert Review Meeting, 21-22 April 2008, Munich, Germany*, IDA Document D-3883 (Alexandria, VA: Institute for Defense Analyses, August 2009); Julia K. Burr et al., *Proceedings of the NATO Nuclear Human Response Subject Matter Expert Review Meeting, 23-25 June 2008, Albuquerque, New Mexico, United States of America,* IDA Document D-3884 (Alexandria, VA: Institute for Defense Analyses, August 2009); Julia K. Burr et al., *Proceedings of the NATO Radiological Human Response Subject Matter Expert Review Meeting, 26 June 2008, Albuquerque, New Mexico, United States of America,* IDA Document D-3885 (Alexandria, VA: Institute for Defense Analyses, August 2009); and Julia K. Burr and Lusine Danakian, *Memorandum for the Record: Meeting Notes – NATO Biological Weapons Subject Matter Expert Human Response Review Meeting* (Alexandria, VA: Institute for Defense Analyses, 16 December 2008).

  - Thomas Sawyer, Defence Research & Development Canada (DRDC) Suffield
  - Ronald Wojtyk, Canadian Forces Health Services Group, Defence Health Services Operations (CFHSG-DHSO)
- Finland
  - Tapio Kuitunen, Centre for Military Medicine, Medical BL Defence & Environmental Unit
- France
  - Fredric Dorandeu, Centre de Recherches du Service Santé des Armées, Ministry of Defence (CRSSA-MOD) French Republic, Toxicology
- Germany
  - Major Nadine Aurbek, Bundeswehr Institute of Pharmacology and Toxicology
  - Stefan Hotop, Elektroniksystem und Logistik-GmbH (ESG)
  - Jacob Rieck, ESG
  - Franz Worek, Bundeswehr Institute of Pharmacology and Toxicology
- Great Britain
  - Lieutenant Colonel David Bates, Defence Medical Services Department, United Kingdom Ministry of Defence (MODUK)
  - Paul Rice, Dstl Porton Down, Biomedical Sciences Department
- Netherlands
  - Paul Brasser, The Netherlands Organization (TNO) Defence, Safety and Security
  - Marijke Valstar, Ministry of Defense (MOD), Military Health Care Expertise Co-ordination Centre
  - Herman Van Helden, TNO Defence, Safety and Security
  - Major George Van Leeuwen, MOD, CBRN Expertise Centre
- United States
  - Major Kevin Hart, Office of the Surgeon General (OTSG), U.S. Army
  - Lieutenant Commander Thomas Herzig, Bureau of Medicine and Surgery (BUMED), Future Plans & Strategies
  - Colonel James Madsen, U.S. Army Medical Research Institute of Chemical Defense (USAMRICD)
  - Major William Pramenko, Joint Chiefs of Staff (JCS/J-8/JRO-CBRND)

  - Sharon Reutter-Christy, Edgewood Chemical Biological Center (ECBC)
  - Jason Rodriguez, Applied Research Associates, Inc. (ARA)
  - Lieutenant Colonel Richard Schoske, U.S. Air Force Surgeon General's Office
  - James Smith, OTSG, U.S. Army
  - Douglas Sommerville, ECBC

The following SMEs were present at both the 23–25 June 2008 nuclear and the 26 June 2008 radiological human response meetings in Albuquerque, New Mexico:

- Canada
  - Commander Ian Torrie, CFHSG-DHSO
  - Diana Wilkinson, DRDC
- France
  - Colonel Yves Chancerelle, French Army Medical Research Centre
- Germany
  - Colonel Dirk Densow, Bundeswehr Medical Office, CBRN Med Defense
  - Stefan Hotop, ESG
  - Jacob Rieck, ESG
- Great Britain
  - Lieutenant Colonel David C. Bates, Defence Medical Services Department, MODUK
  - David Holt, MODUK, Civilian Consultant in Radiation Medicine, Institute for Naval Medicine
  - Robert Jefferson, Newcastle University, The Medical Toxicology Centre
- Netherlands
  - Maarten Huikeshoven, Expertise Center for Military Health Care
- United States
  - Colonel Craig Adams, U.S. Air Force Medical Operations Agency
  - Misuk Choun, OTSG, U.S. Army
  - Major Kevin Hart, OTSG, U.S. Army
  - Colonel Lester Huff, Armed Forces Radiobiology Research Institute (AFRRI)
  - Michael Leggieri Jr., U.S. Army Medical Research & Material Command

  - Gene McClellan, ARA
  - Colonel John Mercier, AFRRI
  - Kyle Millage, ARA
  - Eric Nelson, Defense Threat Reduction Agency (DTRA)
  - James Smith, OTSG, U.S. Army
  - Colonel Clark Weaver, JCS/J-8/JRO-CBRND
  - Captain Edward Woods, U.S. Navy BUMED

The following SMEs were present at the 8–9 May 2008 biological human response meeting in San Lorenzo de El Escorial, Spain:

- Canada
  - Commander Ian Torrie, CFHSG-DHSO
  - Ron Wojtyk, CFHSG-DHSO
- France
  - Francois Thibault, CRSSA-MOD
- Germany
  - Colonel Dirk Densow, Bundeswehr Medical Office, CBRN Med Defense
  - Dmitrios Frangoulichs, Bundeswehr
  - Stefan Hotop, ESG
  - Jakob Rieck, ESG
  - Lothias Zoeller, Bundeswehr
- Great Britain
  - Tim Brooks, Health Protection Agency (HPA)
  - Jackie Duggan, HPA
  - Andy Green, MODUK
  - Stephen Harmer, MODUK
- Netherlands
  - Jacob Boreel, MOD
  - Hugo-Jan Jansen, MOD
- Poland
  - Janusz Kocik, Military Institute of Hygiene and Epidemiology (MIHIE)
- Spain
  - Alberto Cique, NBC Defense School

  - Rene Pita, NBC Defense School

- United States
  - David Brune, OTSG, U.S. Army
  - Ted Cieslak, Department of Defense (DOD), Centers for Disease Control and Prevention (CDC)
  - Stephanie Hamilton, DTRA
  - Major Kevin Hart, OTSG, U.S. Army
  - Lieutenant Commander Thomas Herzig, U.S. Navy BUMED
  - Mark Kortepeter, U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID)
  - Gene McClellan, ARA
  - Major William Pramenko, JCS/J-8/JRO-CBRND
  - Erin Reichert, DTRA
  - Richard Schoske, U.S. Air Force Medical Operations Agency (AFMOA/SG3XH)
  - James Smith, OTSG, U.S. Army

Guidance from the Nations

In the course of developing *AMedP-8*(*C*), guidance from the nations participating in the CBRN Medical Working Group led to the inclusion of several features that were not in previous versions. Since those features are retained in *AMedP-7.5*, it is worth briefly summarizing the nations' requests here.

In contrast to earlier versions of *AMedP-8* that contained collections of fully worked-out casualty estimates based on a range of pre-defined scenarios—the idea being that users would simply pick the scenario that most closely corresponded to their planning scenario—the preference for *AMedP-8*(*C*) was a more flexible methodology so that each nation could (1) use the tools available to it to estimate battlefield challenge levels[27] and (2) tailor the modeled scenario to match its own objectives and capabilities. The nations also requested the capability to consider various factors that could serve to mitigate or exacerbate an individual's Effective CBRN Challenge. While earlier versions of the NATO planning guide considered detection and physical protection, the nations desired to expand the methodology to include activity levels and protection from buildings and vehicles, and to do so in a way that allowed variations among personnel and over time. The methodology for calculating the Effective CBRN Challenge provided in Chapter 3 of *AMedP-7.5* is

[27] Referred to in *AMedP-7-5* as CBRN Challenge.

derived from the process used to develop earlier versions of the methodology but adds the formalism, flexibility, and factors needed to meet these new requirements (some of which are described in Chapter 2 of *AMedP-7.5*).

The *AMedP-7.5* concept for calculating Effective CBRN Challenge was initially presented to the member NATO nations at the *AMedP-8*(*C*) Custodial Meeting in Soesterberg, Netherlands, in June 2007 and formally introduced in Study Draft 2 of *AMedP-8*(*C*) in advance of the 29th CBRN Medical Working Group Meeting in Brussels, Belgium, in February 2008. Discussion at these meetings focused on issues related to the comprehensiveness of the methodology in addressing all parameters desired by the nations, and the level of detail or precision required in characterizing those parameters. *AMedP-7.5* incorporates revisions to the original notation made in response to reviewer comments, but the methodology itself has remained largely unchanged since inception.

Organization

The organization of this TRM largely parallels that of *AMedP-7.5*. As shown in Table 1, which maps major topics to their locations in both *AMedP-7.5* and the TRM, topics mostly appear in the same order in both documents. In some cases, the TRM expands on topics that are not explicitly included in *AMedP-7.5*. In other cases, topics in *AMedP-7.5* are sufficiently addressed there and require no supporting details in the TRM, so there is no corresponding TRM section. In addition to the cross-referencing in Table 1, each TRM chapter title includes the relevant *AMedP-7.5* sections that are addressed in that chapter, and TRM section headings are also marked with the corresponding *AMedP-7.5* section (in green type) when applicable.

Table 1. Cross-References for *AMedP-7.5* and TRM

Topic	*AMedP-7.5*	TRM
Description of the Methodology	Chapter 1	Chapter 2
• Introduction and Document Organization	Section 1.1	N/A*
• Purpose and Intended Use	Section 1.2	N/A*
• Scope	Section 1.3	N/A*
• Definitions	Section 1.4	Section 2.B
• General Assumptions, Limitations, and Constraints	Section 1.5	Section 2.C
• Summary of the Methodology	Section 1.6	N/A*
User Input	Chapter 2	Chapter 3
• Overview of and Default Values for Challenge-Modifying Icon Attributes	Section 2.1.1	Section 3.A
○ Respiratory Minute Volume	Section 2.1.3, Table 2-1	Section 3.A.1

Topic	*AMedP-7.5*	TRM
○ Body Surface Area	Section 2.1.4, Table 2-1	Section 3.A.2
○ IPE (individual protective equipment)	Section 2.1.5, Table 2-1	Section 3.A.3
○ Vehicles and Shelters	Section 2.1.6, Table 2-1	Section 3.A.4
○ Pre-exposure Prophylaxis	Section 2.1.7, Table 2-1	Section 3.A.5
○ Uniform	Section 2.1.8, Table 2-1	Section 3.A.6
○ Aggregate Protection Factor	Section 2.1.9	N/A*
• CBRN Challenge and Effective CBRN Challenge	Section 2.1.2	Section 3.B
• Example Input and Input Schemes	Section 2.1.10	N/A*
• Default Values of Methodology Parameters	Table 2-14	Section 3.C
Calculation of Effective CBRN Challenge	Chapter 3	N/A*
Research Approach for the Development of Agent Models	N/A†	Chapter 4
CRN Human Response and Casualty Estimation	Chapter 4	Chapters 5–17
• CRN Model Framework	Section 4.1	N/A*
○ CRN Injury Profiles	Section 4.1.1	N/A*
○ Assignment of Personnel to Injury Profiles	Section 4.1.2	Section 5.D
○ Casualty Estimation	Section 4.1.3	N/A*
• Chemical Agent Assumptions and Constraint	Section 4.2.1	Section 5.A
• Chemical Agent Toxicity Source Documents	N/A†	Section 5.B
• Transition from AMedP-8(C) Threshold Model to *AMedP-7.5* Probit Model	N/A†	Section 5.C
• Nerve Agent Models (GA, GB, GD, GF, and VX)	Sections 4.2.2 to 4.2.6	Chapter 6
○ Assumptions and Limitations	Sections 4.2.2.2, 4.2.3.2, 4.2.4.2, 4.2.5.2, and 4.2.6.2	Section 6.B
○ Physiological Effects	Tables 4-1, 4-4, 4-7, 4-10, 4-13, and 4-15	Section 6.C
○ Injury Profiles	Tables 4-2, 4-5, 4-8, 4-11, 4-14, and 4-16	Section 6.D
○ Toxicity Parameters	Tables 4-1, 4-4, 4-7, 4-10, 4-13, and 4-15	Section 6.E
○ Medical Treatment	Tables 4-3, 4-6, 4-9, 4-12, and 4-17	Section 6.F

Topic	*AMedP-7.5*	TRM
• HD Model	Section 4.2.7	Chapter 7
○ Assumptions	Section 4.2.7.2	Section 7.B
○ Physiological Effects	Tables 4-19, 4-21, and 4-23	Section 7.C
○ Injury Profiles	Tables 4-20, 4-22, and 4-24	Section 7.D
○ Toxicity Parameters	Tables 4-19, 4-21, and 4-23	Section 7.E
○ Medical Treatment	Table 4-25	Section 7.F
• CG Model	Section 4.2.8	Chapter 8
○ Assumptions	Section 4.2.8.2	Section 8.B
○ Physiological Effects	Tables 4-26 and 4-28	Section 8.C
○ Toxicity Parameters and Concentration Ranges	Tables 4-26 and 4-28	Section 8.D
○ Injury Profiles	Tables 4-27 and 4-29	Section 8.E
○ Medical Treatment	Table 4-30	Section 8.F
• Cl_2 Model	Section 4.2.9	Chapter 9
○ Assumptions	Section 4.2.9.2	Section 9.B
○ Physiological Effects	Table 4-31	Section 9.C
○ Toxicity Parameters	Table 4-31	Section 9.D
○ Injury Profile	Table 4-32	Section 9.E
○ Medical Treatment	Table 4-33	Section 9.F
• NH_3 Model	Section 4.2.10	Chapter 10
○ Assumptions	Section 4.2.10.2	Section 10.B
○ Physiological Effects	Table 4-34	Section 10.C
○ Toxicity Parameters	Table 4-34	Section 10.D
○ Injury Profiles	Table 4-35	Section 10.E
○ Medical Treatment	Table 4-36	Section 10.F
• AC Model	Section 4.2.11	Chapter 11
○ Assumptions	Section 4.2.11.2	Section 11.B
○ Physiological Effects	Table 4-37	Section 11.C
○ Toxicity Parameters	Table 4-37	Section 11.D
○ Injury Profiles	Table 4-38	Section 11.E
○ Medical Treatment	Table 4-39	Section 11.F
• CK Model	Section 4.2.12	Chapter 12
○ Assumptions	Section 4.2.12.2	Section 12.B
○ Physiological Effects	Tables 4-40 and 4-42	Section 12.C
○ Toxicity Parameters and Concentration Ranges	Tables 4-40 and 4-42	Section 12.D
○ Injury Profiles	Tables 4-41 and 4-43	Section 12.E

Topic	*AMedP-7.5*	TRM
○ Medical Treatment	Table 4-44	Section 12.F
• H_2S Model	Section 4.2.13	Chapter 13
○ Assumptions	Section 4.2.13.2	Section 13.B
○ Physiological Effects	Table 4-45	Section 13.C
○ Toxicity Parameters	Table 4-45	Section 13.D
○ Injury Profiles	Table 4-46	Section 13.E
○ Medical Treatment	Table 4-47	Section 13.F
• Radiological Agents (RDDs and Fallout)	Section 4.3	Chapters 14 and 15
○ General Assumptions and Limitations	Section 4.3.1	Section 14.A
○ RDD Assumptions, Limitations, and Constraint	Section 4.3.2.2	Section 15.B
○ RDD Calculation of Effective Doses	Section 4.3.2.3	N/A*
○ Fallout Assumptions, Limitations, and Constraint	Section 4.3.3.2	Section 15.C
○ Fallout Calculation of Effective Doses	Section 4.3.3.3	N/A*
○ Threshold Lethal Dose and Time to Death	Section 4.3.4	Section 14.C
○ Physiological Effects	Tables 4-49 and 4-52	Section 15.E
○ Injury Profiles	Tables 4-50 and 4-53	Section 15.F
○ Dose Ranges	Tables 4-49 and 4-52	Section 15.G
○ Medical Treatment	Tables 4-51 and 4-54	Section 15.H
• Nuclear Effects Assumptions and Limitations	Section 4.4.1	Section 14.B
• Nuclear: Initial Whole Body Radiation	Section 4.4.2	Chapters 14 and 15
○ Assumption	Section 4.4.2.2	Section 15.D
○ Calculation of Effective Dose	Section 4.4.2.3	N/A*
○ Threshold Lethal Dose and Time to Death	Section 4.4.2.4	Section 14.C
○ Physiological Effects	Tables 4-49 and 4-52	Section 15.E
○ Dose Ranges	Tables 4-49 and 4-52	Section 15.F
○ Injury Profiles	Tables 4-50 and 4-53	Section 15.G
○ Medical Treatment	Tables 4-51 and 4-54	Section 15.H
• Nuclear: Blast	Section 4.4.3	Chapter 16
○ Limitations and Constraints	Section 4.4.3.2	Section 16.B
○ Physiological Effects	Table 4-55	Section 16.C
○ Insult Ranges	Table 4-55	Section 16.D
○ Injury Profiles	Table 4-56	Section 16.E
○ Lethal Tertiary Effects	Section 4.4.3.4	Section 16.F
○ Medical Treatment	Table 4-57	Section 16.G

Topic	*AMedP-7.5*	TRM
• Nuclear: Thermal Fluence	Section 4.4.4	Chapter 17
○ Assumptions, Limitations and Constraint	Section 4.4.4.2	Section 17.B
○ Calculation of Effective Insult	Section 4.4.4.3	Section 17.G
○ Physiological Effects	Table 4-60	Section 17.C
○ Insult Ranges	Table 4-60	Section 17.D
○ Injury Profiles	Table 4-61	Section 17.E
○ Medical Treatment	Table 4-62	Section 17.F
Biological Human Response and Casualty Estimation	Chapter 5	Chapters 18–33
• Human Response Submodels	Section 5.1.1	Section 18.B
• Casualty Estimation	Section 5.1.2	N/A*
• Assumptions and Limitations	Section 5.1.3	Section 18.C
• Important Biological Agent Technical References	N/A†	Section 18.D
• Non-Contagious Casualty Estimation	Section 5.1.3	Section 18.E
• Contagious Casualty Estimation	Section 5.1.4	Section 18.F
• Equations Needed to Execute Casualty Estimates	Section 5.1.6	Section 18.G
• Anthrax Model	Section 5.2.1	Chapter 19
○ Assumptions and Limitation	Section 5.2.1.2	Section 19.B
○ Human Response Model	Tables 5-6 to 5-8	Section 19.C
○ Cohorts and Special Considerations	Section 5.2.1.3	Section 19.D
• Brucellosis Model	Section 5.2.2	Chapter 20
○ Assumptions and Limitation	Section 5.2.2.2	Section 20.B
○ Human Response Model	Tables 5-17 to 5-18	Section 20.C
○ Cohorts and Special Considerations	Section 5.2.2.3	Section 20.D
• Glanders Model	Section 5.2.3	Chapter 21
○ Assumptions and Limitation	Section 5.2.3.2	Section 21.B
○ Human Response Model	Tables 5-28 to 5-29	Section 21.C
○ Cohorts and Special Considerations	Section 5.2.3.3	Section 21.D
• Melioidosis Model	Section 5.2.4	Chapter 22
○ Assumptions and Limitation	Section 5.2.4.2	Section 22.B
○ Human Response Model	Tables 5-40 to 5-41	Section 22.C
○ Cohorts and Special Considerations	Section 5.2.4.3	Section 22.D
• Plague Model	Sections 5.2.5 and 5.2.6	Chapter 23
○ Assumptions and Limitation	Section 5.2.5.2 and 5.2.6.2	Section 23.B
○ Human Response Model	Tables 5-48 to 5-50 and 5-56 to 5-57	Section 23.C

Topic	*AMedP-7.5*	TRM
○ Isolation/Quarantine Model Cohorts and Special Considerations	Section 5.2.5.3	Section 23.D
• Q Fever Model	Section 5.2.7	Chapter 24
○ Assumptions and Limitation	Section 5.2.7.2	Section 24.B
○ Human Response Model	Tables 5-59 to 5-61	Section 24.C
○ Cohorts and Special Considerations	Section 5.2.7.3	Section 24.D
• Tularemia Model	Section 5.2.8	Chapter 25
○ Assumptions and Limitation	Section 5.2.8.2	Section 25.B
○ Human Response Model	Tables 5-67 to 5-69	Section 25.C
○ Cohorts and Special Considerations	Section 5.2.8.3	Section 25.D
• Smallpox Model	Sections 5.2.9 and 5.2.10	Chapter 26
○ Assumptions and Limitation	Section 5.2.9.2 and 5.2.10.2	Section 26.B
○ Human Response Model	Tables 5-76 to 5-79 and 5-84 to 5-86	Section 26.C
○ Isolation/Quarantine Model Cohorts and Special Considerations	Section 5.2.9.3	Section 26.D
• EEEV Disease Model	Section 5.2.11	Chapter 27
○ Assumptions and Limitation	Section 5.2.11.2	Section 27.B
○ Human Response Model	Tables 5-87 to 5-88	Section 27.C
○ Cohorts and Special Considerations	Section 5.2.11.3	Section 27.D
• VEEV Disease Model	Section 5.2.12	Chapter 28
○ Assumptions and Limitation	Section 5.2.12.2	Section 28.B
○ Human Response Model	Tables 5-91 to 5-92	Section 28.C
○ Cohorts and Special Considerations	Section 5.2.12.3	Section 28.D
• WEEV Disease Model	Section 5.2.13	Chapter 29
○ Assumptions and Limitation	Section 5.2.13.2	Section 29.B
○ Human Response Model	Tables 5-97 to 5-98	Section 29.C
○ Cohorts and Special Considerations	Section 5.2.13.3	Section 29.D
• Botulism Model	Section 5.2.14	Chapter 30
○ Assumptions and Limitation	Section 5.2.14.2	Section 30.B
○ Human Response Model	Tables 5-104 to 5-106	Section 30.C
○ Cohorts and Special Considerations	Section 5.2.14.3	Section 30.D
• Ricin Intoxication Model	Section 5.2.15	Chapter 31
○ Assumptions and Limitation	Section 5.2.15.2	Section 31.B
○ Human Response Model	Tables 5-121 to 5-122	Section 31.C
○ Cohorts and Special Considerations	Section 5.2.15.3	Section 31.D
• SEB Intoxication Model	Section 5.2.16	Chapter 32
○ Assumptions and Limitation	Section 5.2.16.2	Section 32.B

Topic	*AMedP-7.5*	TRM
○ Human Response Model	Tables 5-129 to 5-130	Section 32.C
○ Cohorts and Special Considerations	Section 5.2.16.3	Section 32.D
• T-2 Mycotoxicosis Model	Section 5.2.17	Chapter 33
○ Assumptions and Limitation	Section 5.2.17.2	Section 33.B
○ Human Response Model	Tables 5-135 to 5-136	Section 33.C
○ Cohorts and Special Considerations	Section 5.2.17.3	Section 33.D
• Ebola Virus Disease Information	Section 5.2.18	Chapter 34
Casualty Summation and Reporting	Chapter 6	N/A*

* The TRM does not discuss this topic because the explanation in *AMedP-7.5* was deemed sufficient.

† *AMedP-7.5* does not discuss this topic because it is not necessary for the execution of the methodology; the topic is discussed in the TRM to provide supporting background information.

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1.2. Definitions, General Assumptions, Limitations, and Constraints (*AMedP-7.5 Chapter 1*)

Introduction

Before beginning a discussion of the *AMedP-7.5* methodology, it is important to understand the terminology. *AMedP-7.5* Section 1.4 defines terms, which were drawn from a variety of sources, used in that document and this TRM. This chapter of the TRM discusses those definitions introduced in *AMedP-7.5* that intentionally differ from those provided in other NATO publications, as well as those that were not previously defined in a NATO publication and that require additional explanation beyond that provided in *AMedP-7.5*. In addition, this chapter addresses the assumptions, limitations, and constraints that shape the methodology, and the rationale for their use. Additional assumptions, limitations, and constraints specific to a particular agent or effect are listed in the agent-specific chapter of the TRM.

Definitions (*AMedP-7.5 Section 1.4*)

Definitions Intentionally Different from Those in Existing NATO Publications

AMedP-7.5 defines two terms differently than other NATO documents: population at risk (PAR) and wounded in action (WIA). This section explains why the existing NATO definitions were insufficient for use in *AMedP-7.5*.

Population at Risk

AMedP-13(*A*)*: NATO Glossary of Medical Terms and Definitions* defines PAR as "a group of individuals exposed to conditions which may cause injury or illness."[28] NATOTerm[29] does not contain a definition. The *AMedP-13*(*A*) definition does not make sense because it implies that everyone in the PAR was *actually exposed*, whereas the more typical usage is that they are *at risk* of exposure. The authors of *AMedP-7.5* defined PAR in the following way: "a group of individuals considered at risk of exposure to conditions which may cause injury or illness. For this methodology, this is always the total number of personnel in the scenario, and is defined by user input." [30] This differs from the *AMedP-13*(*A*) definition in that all units in the scenario are considered, not just those that were exposed to "conditions which may cause injury or illness." In this way, the *AMedP-7.5* casualty rates will reflect the fraction of the units of interest, rather than a fraction of the subset of units that were exposed to a CBRN challenge, that are lost.

Wounded in Action

The second *AMedP-7.5* definition that differs from other NATO publications is WIA:

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28 North Atlantic Treaty Organization (NATO), *AMedP-13*(*A*)*: NATO Glossary of Medical Terms and Definitions*, STANAG 2409 (Brussels: NATO, 6 May 2011), 2-49.

29 https://nso.nato.int/natoterm/content/nato/pages/home.html?lg=en

30 NATO, *AMedP-7.5*, 1-7.

> a battle casualty other than 'killed in action' [KIA] who has incurred an injury due to an external agent or cause as a result of hostile action. Note: The term encompasses all kinds of wounds and other injuries incurred in action, whether there is a piercing of the body, as in a penetrating or perforated wound, or none, as in the contused wound; all fractures, burns, blast concussions, all effects of biological and chemical warfare agents, the effects of exposure to ionizing radiation or any other destructive weapon or agent.[31]

This definition differs from that in NATOTerm, which states that a WIA "has incurred a non-fatal injury," thereby precluding the possibility that a WIA can later die. Since a KIA or DOW (died of wounds) was, by definition, previously WIA, the *AMedP-7.5* definition excludes the "non-fatal" descriptor, which allows individuals to progress from WIA to either fatality category.

Definitions Not Previously Included in Existing NATO Publications

Not all terms will be included. If the definition in *AMedP-7.5* is self-explanatory or sufficient, then no further details will be provided here. For a few terms listed here, however, there is more to say beyond the definition provided in *AMedP-7.5*.

CBRN Challenge

AMedP-7.5 defines CBRN Challenge as:

> The time-varying cumulative amount or degree of CBRN agent or effect estimated to be present in the physical environment with which icons are interacting.
>
> For chemical agents with concentration-based effects, also includes the time-varying instantaneous (non-cumulative) concentration estimated to be present in the physical environment with which icons are interacting.[32]

An important distinction between concentration-based effects for certain chemical agents and the remaining types of CBRN Challenges is that the former must be input as *instantaneous* concentration value over time whereas the latter are *cumulative* estimates of the amount of CBRN agent or effect over time. In other words, a graph of the concentration versus time would increase and decrease over time as the cloud moved over an icon, eventually dropping to zero at the end of the exposure. In contrast, a graph of the (non-concentration-based) CBRN Challenge data over time would be a non-decreasing function that would be at a maximum at the end of the exposure.

The reason for this difference is that the non-concentration-based human response models in *AMedP-7.5* are a function of the total (cumulative) challenge at an icon, whereas the concentration-based human response models are a function of the maximum

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31 NATO, *AMedP-13*(*A*), 2-65.

32 NATO, *AMedP-7.5*, 1-7.

instantaneous concentration at an icon. These two inputs to the methodology are calculated by *AMedP-7.5* Equations 3-1 and 3-2, respectively, which require that the CBRN Challenge be in the forms specified above.

Injury Severity Level

AMedP-7.5 defines Injury Severity Level as "the degree of injury caused by the Effective CBRN Challenge, characterized by five integer levels and corresponding qualitative descriptions, as defined in *AMedP-7.5* Table 1-3. The definitions are expanded from those provided in *AMedP-13*(*A*) to include both medical requirements and operational capability." The Injury Severity Level descriptions are reproduced in Table 2 below.

These terms were originally developed for use in the immediate predecessor version of *AMedP-7.5*, *AMedP-8*(*C*). A review of existing NATO publications at that time revealed that the Injury Severity Level terms in use were vague and did not clearly identify the types of signs and symptoms that would result in each clinical level of severity, an observation that is still true in the current version of *AMedP-13*. Further, the ambiguity of the terms leaves open the possibility for different classifications by different users. *AMedP-13*(*A*) describes four levels of clinical severity—slight, moderate, serious, and very serious. These definitions are shown in Table 3.

Table 2. Injury Severity Level Definitions

	Degree	Description
0	N.O.I.*	Although some exposure to an agent or effect may have occurred, no observable injury (as would be indicated by manifested symptoms) has developed. Alternately, recovery from a prior injury is complete.
1	Mild	Injury is manifesting symptoms (and signs for biological agents) of such severity that individuals can care for themselves or be helped by untrained personnel. Condition may not impact ability to conduct the assigned mission.
2	Moderate	Injury is manifesting symptoms (and signs for biological agents) of such severity that medical care may be required. General condition permits treatment as outpatient and some continuing care and relief of pain may be required before definitive care is given. Condition may be expected to interrupt or preclude ability to conduct the assigned mission.
3	Severe	Injury is manifesting symptoms (and signs for biological agents) of such severity that there is cause for immediate concern but there is no imminent danger to life. Individual is acutely ill and likely requires hospital care. Indicators are questionable—condition may or may not reverse without medical intervention. Individual is unable to conduct the assigned mission due to severity of injury.
4	Very Severe	Injury is manifesting symptoms (and signs for biological agents) of such severity that life is imminently endangered. Indicators are unfavorable—condition may or may not reverse, even with medical intervention. Prognosis is death without medical intervention. Individual is unable to conduct the assigned mission due to severity of injury.

* N.O.I. = No Observable Injury

Table 3. *AMedP-13*(*A*) Severity Level Degrees and Descriptions

Degrees	Description
Slightly	Minor severity of illness, disease or trauma, such that only minor medical care is needed, such as bandages and wound cleansing
Moderately	Intermediate severity of illness, disease or trauma of such a degree that medical care is needed, but there is no cause for immediate concern
Seriously	Illness, disease or trauma of such severity that there is cause for immediate concern but there is no imminent danger to life
Very Seriously	Illness, disease or trauma of such severity that life is imminently endangered

Source: NATO, *AMedP-13*(*A*), 2-13.

AMedP-6(*B*), *NATO Handbook on the Medical Aspects of NBC Defensive Operations,* defined four triage levels as shown in Table 4. The definitions focus on the level of medical care required for individuals.

Table 4. *AMedP-6*(*B*) Triage Severity Level Degrees and Descriptions

Category	Triage Level	Description
Immediate treatment	T1	This includes those requiring emergency lifesaving treatment. Treatment should not be time consuming or require numerous, highly trained personnel, and the casualty should have a high chance of survival with therapy.
Delayed treatment	T2	The general condition permits some delay in therapy although some continuing care and relief of pain may be required before definitive care is given.
Minimal treatment	T3	This includes those with relatively minor signs and symptoms who can care for themselves or who can be helped by untrained personnel.
Expectant treatment	T4	This group is comprised of patients whose treatment would be time consuming, require numerous highly trained people, who have life threatening conditions beyond the treatment capabilities of the medical unit, and would have a low chance of survival. It must be noted that the decision to place a casualty in the expectant category is not necessarily a decision to render no therapy. Rather, the triage categories determine the priority in which casualties are treated.

Source: NATO. *AMedP-6*(*B*)*: NATO Handbook on the Medical Aspects of NBC Defensive Operations*, STANAG 2500 (Brussels: NATO, 1 February 1996), 11-4. Although this STANAG has been canceled, the definitions are worth considering.

A review of non-NATO literature included military texts and field manuals, medical texts and journals, and other open sources of material. That review identified then-current descriptions and terminology for injury severity. Other terms were used by the military services, within the triage spectrum, and by hospitals to define the clinical severity of illness, but only a few of these terms helped clarify the operational impacts also associated with the clinical disease severity.

Similar to *AMedP-6*(*B*), the United States Army Institute of Surgical Research's (USAISR) *Emergency War Surgery – 3rd U.S. Revision* used triage categories as well. The definitions, however, varied slightly from those proposed in the NATO manual. That set of categorizations classified individuals in terms of the level of medical, and specifically surgical, intervention required. Further, it provided examples at each level of types of injuries that might result in an individual being placed in a specific category. The definitions are shown in Table 5.

Table 5. *Emergency War Surgery* Triage Severity Level Degrees and Descriptions

Title	Description
Immediate	This group includes those soldiers requiring lifesaving surgery. The surgical procedures in this category should not be time consuming and should concern only those patients with high chances of survival (e.g., respiratory obstruction, unstable casualties with chest or abdominal injuries, or emergency amputation).
Delayed	This group includes those wounded who are badly in need of time-consuming surgery, but whose general condition permits delay in surgical treatment without unduly endangering life. Sustaining treatment will be required (e.g., stabilizing IV fluids, splinting, administration of antibiotics, catheterization, gastric decompression, and relief of pain). (The types of injuries include large muscle wounds, fractures of major bones, intra-abdominal and/or thoracic wounds, and burns less than 50% of total body surface area (TBSA).
Minimal	These casualties have relatively minor injuries (e.g., minor lacerations, abrasions, fractures of small bones, and minor burns) and can effectively care for themselves or can be helped by nonmedical personnel.
Expectant	Casualties in this category have wounds that are so extensive that even if they were the sole casualty and had the benefit of optimal medical resource application, their survival would be unlikely. The expectant casualty should not be abandoned, but should be separated from the view of other casualties. Expectant casualties are unresponsive patients with penetrating head wounds, high spinal cord injuries, mutilating explosive wounds involving multiple anatomical sites and organs, second and third degree burns in excess of 60% TBSA, profound shock with multiple injuries, and agonal respiration. Using a minimal but competent staff, provide comfort measures for these casualties.

Source: U.S. Army Institute for Surgical Research, *Emergency War Surgery: Third United States Revision* (Washington, DC: Borden Institute, 2004), 3.2.

The American Hospital Association (AHA), in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and in coordination with the Department of Health and Human Services (HHS), provided guideline terms to define individual clinical severity levels. In particular, these terms were to be used in describing patient status for media and other non-family information requestors in an effort to protect the privacy of the patient. The AHA used five levels as shown in Table 6.

Table 6. AHA Clinical Severity Level Degrees and Descriptions

Title	Description
Undetermined	Patient is awaiting physician and/or assessment
Good	Vital signs are stable and within normal limits. Patient is conscious and comfortable. Indicators are excellent
Fair	Vital signs are stable and within normal limits. Patient is conscious, but may be uncomfortable. Indicators are favorable
Serious	Vital signs may be unstable and not within normal limits. Patient is acutely ill. Indicators are questionable
Critical	Vital signs are unstable and not within normal limits. Patient may be unconscious. Indicators are unfavorable

Source: American Hospital Association, "Media Advisory: HIPAA Updated Guidelines for Releasing Information on the Condition of Patients" (Chicago, IL: Society for Healthcare Strategy and Market Development of the American Hospital Association, 1 February 2003), http://www.aha.org/aha/advisory/2003/030201-media-adv.html.

Using all of the definitions described, new terms and definitions were developed to assess both the medical requirements and operational capability of an individual following an event. The terms were intended to be general enough such that they could be applied to any CBRN-induced illness or injury, but precise enough so as to reduce confusion about the classification of personnel based on their disease and associated symptoms (and signs for biological agents). The injury severity terms in *AMedP-7.5* (which are those originally developed for *AMedP-8*(*C*) with one modification to the "Very Severe" definition explained below) are intentionally different from, although similar to, those proposed in *AMedP-13*(*A*), to preclude the potential for confusion between the clinical severity levels and the disease severity levels to be used for casualty estimation purposes. The injury severity definitions, which are shown in Table 2 and elaborated on below, were discussed and agreed to by SMEs at a series of review meetings on human response.[33]

No Observable Injury (Injury Severity Level 0): "Although some exposure to an agent or effect may have occurred, no observable injury (as would be indicated by manifested symptoms) has developed. Alternately, recovery from a prior injury is complete." This means that the average individual has not developed observable symptoms (and signs for biological agents) associated with injury. The individual may not have been exposed, may have been exposed at levels lower than the lowest observable effect level, or may be in the latent period before symptoms develop. After the injury progression, symptom severity levels may decrease back to the "no observable injury" level. Because the *AMedP-7.5* methodology assumes good health before CBRN exposure, "no observable injury" may be considered equivalent to an individual feeling that he or she is in "perfect

33 Burr et al., *Chemical Human Response*; Burr et al., *Nuclear Human Response*; and Burr et al., *Radiological Human Response*.

health"; there is no need for even self-medicated intervention and no deterioration of mission capability.

Mild (Injury Severity Level 1): "Injury is manifesting symptoms (and signs for biological agents) of such severity that individuals can care for themselves or be helped by untrained personnel. Condition may not impact ability to conduct the assigned mission." Mild injury progression includes "nuisance" symptoms—the types of symptoms (and signs for biological agents) that might not prompt an individual to seek medical attention or miss work. These include symptoms for which an individual might self-medicate, including but not limited to, runny nose (rhinorrhea), slightly blurry vision, indigestion or heartburn, nausea, abdominal pain, and slight cough or tightness in the chest. These symptoms would not be expected to significantly affect an individual's ability to accomplish most mission tasks. In the event of a known or suspected CBRN event, these symptoms would indicate the potential for an injury progression of increasing severity, however, and therefore might be considered (depending on national or NATO policy) to be a basis for an individual's removal from operations and transfer to the medical system.

Moderate (Injury Severity Level 2): "Injury is manifesting symptoms (and signs for biological agents) of such severity that medical treatment may be required. General condition permits treatment as outpatient and some continuing care and relief of pain may be required before definitive care is given. Condition may be expected to interrupt or preclude ability to conduct the assigned mission." Moderate symptoms (and signs for biological agents) include those that might cause an individual to seek medical intervention or treatment as an outpatient. These have the potential to interrupt or otherwise affect an individual's ability to complete assigned mission tasks. Symptoms of moderate severity level might include sore skin or small blisters, vomiting, respiratory congestion (bronchorrhea) or difficulty breathing, ocular sensitivity to light, frequent diarrhea, difficulty concentrating, or trembling muscles.

Severe (Injury Severity Level 3): "Injury is manifesting symptoms (and signs for biological agents) of such severity that there is cause for immediate concern but there is no imminent danger to life. Individual is acutely ill and likely requires hospital care. Indicators are questionable—condition may or may not reverse without medical intervention. Individual is unable to conduct the assigned mission due to severity of injury." Severe symptoms may include, but are not limited to, the following: large blisters, temporary blindness, extreme headache, hemoptysis, uncontrollable diarrhea, disorientation, and sporadic convulsions. These symptoms (and signs for biological agents) will affect an individual's ability to perform assigned tasks and likely will result in a requirement for inpatient care for some duration. It is unclear, based solely on the symptoms, what an individual's prognosis will be, although none of the symptoms, even in combination, may be expected to pose an imminent danger to life.

Very Severe (Injury Severity Level 4): "Injury is manifesting symptoms (and signs for biological agents) of such severity that life is imminently endangered. Indicators are unfavorable—condition may or may not reverse even with medical intervention. Prognosis is death without medical intervention. Individual is unable to conduct the assigned mission due to severity of injury." The symptoms (and signs for biological agents) classified as "very severe"—paralysis, unconsciousness, prostration, or respiratory failure—will result in the death of an individual if allowed to continue for some period of time unabated and without medical intervention.[34] These symptoms will affect the individual's ability to complete the assigned mission tasks and, in the event of death, will preclude any future mission capability.

Note that this definition has been slightly modified from the version published in *AMedP-8*(*C*), which the SMEs agreed to. That version, the end of which read (emphasis added) "individual is unable to conduct the assigned mission *and is unexpected to return to the mission* due to severity of injury," was changed to allow for individuals to return to duty (RTD) after having received medical treatment, which was excluded from the versions of the methodology before *AMedP-7.5*.

General Assumptions, Limitations, and Constraints (*AMedP-7.5 Section 1.5*)

AMedP-7.5 includes a number of assumptions, limitations, and constraints to enable data and concepts previously established for other models to be incorporated into the *AMedP-7.5* methodology. Ideally, the assumptions simplify the methodology and make the representations and estimation of casualties easier for the user to understand. The limitations and constraints help define the scope of the methodology, with limitations specifying things outside the scope and constraints specifying things within the scope.

This section is intended to elucidate some of the reasoning behind many of the assumptions, limitations, and constraints and to further describe their effect on the casualty estimates output by the methodology. The assumptions, limitations, and constraints stated in *AMedP-7.5* are provided here as they appear in the NATO document. Each is formatted in block quote and followed by the associated rationale.

[34] For modeling purposes, SMEs agreed that remaining at Severity Level 4 as a result of exposure to CRN agents/effects and exhibiting very severe respiratory, muscular, neurological, or other symptoms for a period exceeding 15 minutes (without medical attention) would result in an individual becoming a fatality.

Assumption: Individuals are normally healthy—they have no pre-existing physiological injury or condition that would alter human response.

The methodology assumes that individuals are normally healthy. In other words, they have no pre-existing physiological injuries or physiological conditions that would be expected to increase susceptibility and alter human response or contribute increased risk factors. If casualty estimation is being done for populations that are already ill or susceptible to the CBRN agents or effects, then this assumption will result in an underestimation of casualties. In the same manner, this methodology may not be suitable for estimating casualties among civilian populations, since civilian populations may be more susceptible to CBRN agents or effects.

SMEs agreed that individuals should be considered normally healthy. The consideration of pre-existing physiological injuries or physiological conditions would likely increase susceptibility, alter human response, contribute increased risk factors, and generally complicate the human response and casualty estimation.

Assumption: Human response begins after the challenge ends—each icon receives its entire Effective CBRN Challenge prior to the onset of any symptoms, and there is a common "time zero" at which human response begins for every individual in the scenario.

This assumption has two important implications. First, it allows the appropriate Injury Profile to be determined by the total Effective CBRN Challenge, the calculation of which necessitates that the challenge has already ended. Second, it simplifies the determination of when icons begin following the Injury Profiles, establishing a common time across all icons. Because the casualty reporting time steps are in units of days, any differences between the times at which human response would begin for different icons would be operationally insignificant.

Assumption: Parameter values derived from *animal models* are applicable to *human* response models and casualty estimation (in most cases, the animal model used was a non-human primate).

This assumption allows the human response to a CBRN agent or effect to be modeled directly from animal data without an extrapolation or correction factor. At this time, there are insufficient data to quantitatively describe the variation in responses among species, so no variation is assumed. Future modeling efforts may incorporate an extrapolation factor to account for differences among species as data become available to support such a modification.

Assumption: Medical treatment facilities have unlimited resources.

The methodology assumes that all casualties entering the medical system will receive the same level of care without consideration for any personnel or equipment limitations,

which would likely affect the level of care available in a mass casualty incident. The methodology does not modify the treated casualty estimate to account for any shortfalls between the estimated medical requirements and the available capabilities.

Limitation: Explosive trauma casualties are not considered.

Although chemical, biological, or radiological agents could be disseminated by means of explosives, the human response modeled in *AMedP-7.5* is a function only of the agents themselves. Additional injuries caused by the means of agent delivery could be modeled separately using conventional explosive trauma models, but the user is cautioned to avoid double-counting.

Limitation: Casualties resulting from secondary/indirect effects such as battle stress, burns due to secondary fires, and opportunistic infections, are not considered.

Although it is recognized that these phenomena could be important—particularly battle stress—they are too complicated to be included in the model; this limitation is intended to simplify.

Limitation: The potential for administrative declaration of "casualties" or delay of RTD out of precaution is not considered.

It is recognized that in cases of known or suspected CBRN exposure, a commander may decide to withdraw personnel and have them monitored at a medical treatment facility (MTF), even if none or few have definite symptoms, or the commander may decide to hold them for monitoring at the MTF after their symptoms have disappeared. Particularly since the effects of some agents/effects may be delayed for hours before the onset of life-threatening symptoms and the agent identity might be unknown in a real-world situation, this is a prudent course of action. However, since the methodology is *symptom based*, it does not account for administrative decisions to declare a person an "asymptomatic casualty" or to delay RTD.

Constraint: For inhalation challenges, the methodology uses an estimated inhaled challenge, rather than an estimated retained challenge.

This is a reflection of the data underlying the Injury Profiles for inhalation challenges. Controlled studies generally measured the inhaled challenge and the associated physiological response. Therefore, the proportion of the challenge that is retained in the body is irrelevant to estimating the human response from these data.

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1.3. User Input and Default Parameter Values (*AMedP-7.5 Chapter 2*)

This chapter discusses the rationales for decisions related to *AMedP-7.5* Chapter 2 topics, namely default values for icon attributes, CBRN Challenge units, and user-specifiable parameters.

Overview of and Default Values for Challenge-Modifying Icon Attributes (*AMedP-7.5 Section 2.1.1*)

AMedP-7.5 Table 2-1 specifies various challenge-modifying icon attributes (minute volume, body surface area (BSA), IPE, vehicle or shelter, pre-exposure prophylaxis, and uniform), and the CBRN Challenge types to which each applies in the methodology. In addition, default values are listed for certain icon attributes. This section discusses each challenge-modifying icon attribute and justifies its default value (if any) and its relevance to the different challenge types.

Five of the six icon attributes correspond to CBRN Challenges calculated using *AMedP-7.5* Equation 3-1. Minute volume and BSA can modify these challenges through the Z variable in that equation. IPE, vehicle or shelter, and pre-exposure prophylaxis can modify the challenge through the APF (Aggregate Protection Factor) variable. Uniform is an icon attribute that uniquely modifies the estimate of thermal fluence, which is calculated according to *AMedP-7.5* Equation 4-38 rather than Equation 3-1.

Minute Volume (*AMedP-7.5 Section 2.1.3 and Table 2-1*)

The *AMedP-7.5* methodology models minute volume as a challenge-modifying icon attribute for chemical, biological, and radiological inhalation challenges. Since other challenge types are not dependent on minute volume, this attribute is not modeled to modify challenges for icons that are exposed to chemical percutaneous vapor or liquid, whole-body or percutaneous radiation, or nuclear blast or thermal challenges.

For agents that are inhaled, the variable Z (in AMedP-7.5 Equation 3-1) is defined as a function of minute volume, or the volume of air inhaled by an individual per unit time. Minute volumes in turn are a function of exertion. The methodology allows the user to assign each icon a minute volume that corresponds to the activity level associated with the task the individuals in that icon are performing. A brief survey of available literature provided various values for minute volumes associated with different activity levels. The results of this survey are shown in Table 7.

Table 7. Summary of Minute Volumes from Literature

	Adult Male Minute Volumes (L/min)			Adult Female Minute Volumes (L/min)		
Activity Level	**Source 1**	**Source 2**	**Source 3**	**Source 1**	**Source 2**	**Source 3**

Rest	7	N/A	9	5.4	N/A	6.4
Light Activity	15	14	26	12	8	20.8
Moderate Activity	30	41	N/A	24	26	N/A
Heavy Activity	74	80	49.4	59	48	46.2

1 David W. Layton, "Metabolically Consistent Breathing Rates for Use in Dose Assessments," *Health Physics* 64, no. 1 (1993): 23–36.

2 J. H. Overton and R. C. Graham, *Predictions of Ozone Absorption in Human Lungs from Newborn to Adult*, EPA-68-02-4450 (Research Triangle Park, NC: U.S. Environmental Protection Agency, 1989).

3 Jack Valentin, ed., "Basic Anatomical and Physiological Data for Use in Radiological Protection: Reference Values," *Annals of the ICRP Publication* 32, no. 3–4 (2003). ICRP Publication 89.

Layton's values (source 1 for Table 7) provided minute volumes for the widest range of activity levels, and the light activity value for adult males (15 liters/minute) is consistent with the default minute volume used in many hazard prediction models. Hence these values were adapted for use in the development of the illustrative examples. AMedP-7.5 uses a value of 7.5 liters/minute for the "at rest" activity level and 75 liters/minute for the heavy activity level, which allows the light through heavy activity levels to be integer multiples of the "at rest" value, simplifying some calculations.

As shown in *AMedP-7.5* Table 2-2, the biological human response models require inputs in the form of dose, meaning some number of organisms, plaque forming units (PFUs), colony forming units (CFUs), or quantity of mass. The CBRN Challenge values for aerosol particulates and chemical vapor are expressed in terms of some measured quantity of agent per minute per unit of volume—for example, mg-min/m^3. Use of a Z factor expressed as volume per minute will result in a calculated dose expressed in the appropriate units.

The chemical human response models, however, require inputs in the form of concentration time (Ct), not dose. The chemical toxicity models that underlie the inhaled chemical vapor Injury Profiles express toxicity in terms of Ct, but use the assumption that individuals are breathing at a rate of 15 liters/minute,[35] the light activity minute volume shown in Table 7. To modify a chemical vapor challenge to account for activity level while retaining outputs in the appropriate units, minute volumes were simply scaled to the light activity level. In other words, Z for inhaled chemical vapor is simply the ratio of the minute volume for the desired activity level to the assumed minute volume of 15 liters/minute. Z values of 0.5, 1, 2, and 5 were assigned based on this method for at rest, light, moderate, and heavy activity, respectively.

35 See Chapters 4 and 5 of this document for further discussion of the derivation of inhaled chemical vapor Injury Profiles.

Body surface area (*AMedP-7.5 Section 2.1.4 and Table 2-1*)

The *AMedP-7.5* methodology models BSA as a challenge-modifying icon attribute only for chemical percutaneous liquid challenges. This is because the human response to this route of exposure is a function of surface area exposed. Accordingly, the CBRN Challenge units are mg/m^2, which must be multiplied by the BSA exposed to calculate the Effective CBRN Challenge in the appropriate units of mg.

The determination of an appropriate default value for Z depends on two parameters: the BSA of a typical NATO soldier and the expected fraction of a soldier's BSA that is exposed in an attack. The *Radiological Health Handbook* "standard man" has a BSA of 1.8 m^2.[36] A brief review of the literature confirmed this value as reasonable, with mean BSA values for adult males ranging from 1.73 to 1.91. Many different empirical equations have been derived independently over the past century to calculate BSA, and all are direct functions of an individual's height and weight.[37] Consequently, calculated BSA values vary by sex, fitness level, age, and nationality, because these are all correlated to height and weight. Selected mean BSA values from the literature for various combinations of these factors are listed in Table 8; when segregating the data was possible, young male adults of normal fitness level (as opposed to overweight or obese) were chosen from the larger study samples because they are most representative of NATO soldiers. For consistency with the "standard man" weight assumption and the range of mean BSA values in the literature, a BSA value of 1.8 m^2 was chosen as the default.

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36 U.S. Department of Health, Education, and Welfare, *Radiological Health Handbook, Revised Edition* (Rockville, MD: U.S. Department of Health, Education, and Welfare, January 1970), 215.

37 See various formulas in the following papers: Chi-Yuan Yu, Yu-Hung Lo, and Wen-Ko Chiou, "The 3D Scanner for Measuring Body Surface Area: A Simplified Calculation in the Chinese Adult," *Applied Ergonomics* 34, no. 3 (2003): 273–278; Johan Verbraecken, Paul Van de Heyning, Wilfried De Backer, and Luc Van Gaal, "Body Surface Area in Normal-weight, Overweight, and Obese Adults. A Comparison Study," *Metabolism* 55, no. 4 (2006): 515–524.

Table 8. BSA Estimates from the Literature

Reference	Fitness	Study Location	BSA Formula[a]	n	Sex	Age	Mean BSA
Dooley et al.	Unknown	Australia	DuBois and DuBois	1434	Male	19–102 (mean 61)	1.89
Sacco et al.	Unknown	UK	DuBois and DuBois	1471	Male	Unknown	1.91
Verbraecken et al.	Normal	Belgium	Mosteller	289	Male	Unknown	1.88
———			DuBois and DuBois	289	Male	Unknown	1.88
———			Boyd	289	Male	Unknown	1.87
———			Gehan and George	289	Male	Unknown	1.89
———			EPA	289	Male	Unknown	1.88
———			Hayrock et al.	289	Male	Unknown	1.88
———			Mattar	289	Male	Unknown	1.88
———			Livingston and Scott	289	Male	Unknown	1.86
———			Yu et al. (1)	289	Male	Unknown	1.79
Yu et al.	Unknown	China	Yu et al. (2)	69	Male	20–31	1.73
———			Yu et al. (3)	863	Male	32–51	1.73

*Note: S*ee Appendix B for full reference citations

[a] BSA = body surface area (m^2); H = height in centimeters; W = weight in kilograms.
DuBois and DuBois: BSA = $0.00718 \times H^{0.725} \times W^{0.425}$
Mosteller: BSA = $[(H \times W)/3600]^{0.5}$
Boyd: BSA = $0.0178 \times H^{0.5} \times W^{0.484}$
Gehan and George: BSA = $0.0235 \times H^{0.42246} \times W^{0.51456}$
EPA: BSA = $0.0239 \times H^{0.417} \times W^{0.517}$
Hayrock et al.: BSA = $0.024265 \times H^{0.5378} \times W^{0.3964}$
Mattar: BSA = $(H + W - 60)/100$
Livingston and Scott: BSA = $0.1173 \times W^{0.6466}$
Yu et al. (1): BSA = $0.015925 \times (H \times W)^{0.5}$
Yu et al. (2): BSA = $0.016091 \times (H \times W)^{0.5}$
Yu et al. (3): BSA = $0.015966 \times (H \times W)^{0.5}$

Given that the orientation of personnel relative to the chemical challenge in scenarios is unknown, the fraction of an individual's BSA that is exposed was assumed to be one-half. As a result, the default value of Z is $0.5 \times 1.8\ m^2 = 0.9\ m^2$.

By default, BSA is not modeled as a challenge-modifying icon attribute for chemical percutaneous vapor because it is assumed that the entire body is exposed. Note that this challenge-modifying icon attribute is independent from individual protective equipment, which is discussed next. BSA should not be reduced in an effort to account for individual

protective equipment that covers a fraction of the body, as that is already factored into the IPE protection factors.

IPE (*AMedP-7.5 Section 2.1.5 and Table 2-1*)

Individual protective equipment can protect against certain types of CBRN Challenges. *AMedP-7.5* Table 2-4 presents suggested values for various types of IPE. For inhalation challenges, a value of 1 (no protection) was chosen for IPE classes offering no respiratory protection. For IPE classes with respiratory protection, a value of 100,000 was chosen based on test data for the Joint Service General Purpose Mask using corn oil aerosol (mass median aerodynamic diameter between 0.522 and 0.540 µm) as a simulant for C/B agents. That is, the participants performed various exercises while wearing masks, and the degree to which the corn oil aerosol penetrated the mask was measured.[38] In over 83% of cases, the protection factor was greater than 100,000 (the highest the experimenters could measure), and in over 96% of cases the value was greater than 20,000. The average of all the reported values (n = 1200) was 90,363; since this value is artificially *lowered* due to the maximum measurable value being 100,000, the minimum value one could reasonably choose would be 90,000. We chose 100,000 because the average certainly was higher than 90,000, with the constraint that we do not know how much higher because of experimental measurement limitations.

For chemical vapor and liquid challenges, protection factor values were chosen to reflect the percentage of the BSA that is protected by the IPE class. Table 9 lists estimates of the fractions of total BSA represented by various regions of the body. These values were derived from the "rule of nines" common in burn management literature, with a slight modification based on the estimate that the hands each make up approximately 1% of the BSA.[39]

Table 9. Fraction of Total BSA for Various Parts of the Body

Part of Body	Fraction of Total BSA (%)
Head/neck	9.0
Torso	36.5
Legs	36.5
Arms	16.0

38 U.S. Army Research, Development and Engineering Command, memorandum to Mr. Kevin Puckace, 6 October 2006, "Protection Factor Testing of the Joint Service General Purpose Mask (JSGPM) Multi-Service Operational Test and Evaluation (MOT&E) Conditioned 5.5 PPHR Faceblank Formulation Low Rate Initial Production (LRIP) Masks."

39 Saraf, S., and S. Parihar, "Burns Management: A Compendium," *Journal of Clinical and Diagnostic Research* 1, no. 5 (2007): 426–36; and Rhodes, J., C. Clay, and M. Phillips, "The Surface Area of the Hand and the Palm for Estimating Percentage of Total Body Surface Area: Results of a Meta-analysis," *British Journal of Dermatology* 169, no. 1 (2013): 76–84.

Hands	2.0

For the mask-only IPE class, approximately half of the head/neck region is protected from percutaneous vapor and liquid challenges (approximately 4.5% of the total BSA), so the corresponding protection factor is 100/95.5 ≈ 1.05. When wearing the suit and boots, approximately 89% of the total BSA is protected (all but the hands and head/neck), corresponding to a protection factor of 100/11 ≈ 9.1. With the addition of a mask, an additional 4.5% BSA is protected, increasing the protection factor to 100/6.5 ≈ 15.4. With the further donning of gloves and a hood, individuals are fully protected against all chemical percutaneous vapor and liquid challenges, which can be modeled with a protection factor of infinity. As specified in a footnote to *AMedP-7.5* Table 2-4, IPE does not truly offer infinite protection but is typically designed to protect against a 10 g/m^2 challenge, which refers to a military specification for liquid chemical agents for the U.S. Joint Service Lightweight Integrated Suit Technology (JSLIST).[40]

For cutaneous beta radiation, suggested IPE protection factors are infinity for the full protection IPE class and 1 (no protection) for all other IPE classes. This is to reflect the assertion that any exposed skin will result in cutaneous radiation injury, resulting in the symptoms described in the cutaneous Injury Profiles. The BSA affected by the radiation injury is not a factor in determining casualty status in the methodology.

AMedP-7.5 Table 2-1 specifies a default value of "None" for IPE, which would reflect the IPE status of military personnel not anticipating the imminent threat of a CBRN attack. If personnel were in another IPE class, or if the IPE class were expected to change over time, then the user should select an IPE class other than the default value.

Vehicles and shelters (physical protection and ColPro) (*AMedP-7.5 Section 2.1.6 and Table 2-1*)

The vehicles or buildings individuals occupy may also mitigate the CBRN Challenge due to aerosol, radiation, thermal, and blast effects. Collective protection (ColPro) for vehicles and shelters utilizes overpressure and air filtration to protect individuals from aerosol challenges. The extent to which an individual's CBRN Challenge is mitigated by the physical protection and ColPro provided by vehicles and shelters is captured in the methodology as protection factors, which can vary by icon and time step.

For inhalation and percutaneous vapor protection afforded by vehicles and shelters, protection ($PF_{V\text{-}SH,Q,n}$) is calculated as a function of the air exchange rate, the duration of occupancy ($Occupancy_n$), and the duration the vehicle or shelter is enveloped in the cloud ($Duration_n$) as detailed in *AMedP-7.5* Equation 2-1. A brief survey of available literature

40 Defense Logistics Agency (DLA), *Joint Service Lightweight Integrated Suit Technology* (*JSLIST*) *Coat and Trouser, Chemical Protective*, MIL-DTL-32102 (Philadelphia, PA: DLA Troop Support, Clothing and Textiles Directorate, 3 April 2002), 4.

produced widely varying values for air exchange rates associated with buildings and vehicles of various types. Table 10 summarizes these values;[41] it also provides sample calculations of protection factors based on the assumption that $\text{Duration}_n = \text{Occupancy}_n =$ 0.25 hr. The air exchange rate values listed in *AMedP-7.5* Table 2-5 were chosen from the ranges provided in Table 10.

Table 10. Summary of Air Exchange Rates from Literature

Building/Vehicle Type	Air Exchange Rate (ACH)	Time Building is Exposed (hr)	Time of Occupancy from Cloud Arrival (hr)	Protection Factor
Residential Building (Windows Closed)[a]	0.53 0.08–3.24	0.25 0.25	0.25 0.25	15.8 100.7–3.2
Residential Building (Windows Open)[a]	6.4	0.25	0.25	2.0
Nonresidential Building[a]	1.285 0.3–4.1	0.25 0.25	0.25 0.25	6.9 27.3–2.7
Vehicle[a]	36	0.25	0.25	1.1
Mass-Transit Vehicle[a]	1.8–5.6	0.25	0.25	5.1–2.2
Stationary Automobile[b]				
Windows Close/No Ventilation	1.0–3.0	0.25	0.25	8.7–3.4
Windows Closed/Fan on Recirculation	1.8–3.7	0.25	0.25	5.1–2.9
Windows Open/No Ventilation	13.3–26.1	0.25	0.25	1.4–1.2
Windows Open/Fan on Fresh Air	36.2–47.5	0.25	0.25	1.1

[a] Ted Johnson, *A Guide to Selected Algorithms, Distributions, and Databases used in Exposure Models Developed by the Office of Air Quality Planning and Standards* (Chapel Hill, NC: TRJ Environmental, Inc., 22 May 2002), http://www2.epa.gov/sites/production/files/2013-08/documents/report052202.pdf. Accessed 23 November 2015.

[b] J. H. Park et al., "Measurement of Air Exchange Rate of Stationary Vehicles and Estimation of In-Vehicle Exposure," *Journal of Exposure Analysis & Environmental Epidemiology* 8, no. 1 (January–March 1998): 65–78.

AMedP-7.5 Table 2-6 lists suggested vehicle and shelter protection factors for inhalation and percutaneous challenges. For collectively protected vehicles and shelters, an inhalation and percutaneous vapor protection factor value of 3,000 was selected on the assumption that collective protection would be equivalent to that provided by high

41 Table 10 source 1 listed only summary statistics for each building/vehicle type, which are reproduced here. For residential buildings (windows closed) and nonresidential buildings, the point estimates are geometric mean values of the lognormal distribution fit to the data, and the ranges beneath them represent the minimum and maximum values of the underlying data. For residential buildings (windows open) and vehicles (generally), only point estimates were available.

efficiency particulate air (HEPA) filters. Since HEPA filters are designed to remove 99.97% of airborne particles measuring 0.3 microns or greater in diameter,[42] this means approximately 1 in 3,000 particles would penetrate the system; alternatively, with HEPA filtration, 3,000 times as many particles would be required to result in a hazard equivalent to that experienced in the absence of filtration. Vehicles and shelters (whether collectively protected or not) were assumed to be completely protective against percutaneous liquid chemical challenges.

AMedP-7.5 Table 2-7 provides notional protection factor values for neutron and gamma radiation. These values were converted from transmission factors (the inverse of protection factors) published in the earliest version of *AMedP-8*, and the production documentation for that methodology specifies that the transmission factors "were developed by randomly modifying classified factors provided by the U.S. Army Nuclear and Chemical Agency."[43]

AMedP-7.5 Table 2-1 specifies a default value of "None" for vehicles or shelters, which would result in a conservative estimate of casualties for military personnel not dismounted or in a foxhole, because any vehicle or shelter is likely to offer some level of protection. Users can opt to use any other vehicle or shelter if the default value is not appropriate for all icons.

Pre-exposure prophylaxis (*AMedP-7.5 Section 2.1.7 and Table 2-1*)

Certain pre-exposure prophylaxes, such as bioscavengers, could also be modeled to reduce the CBRN Challenge by some factor. Although none of the agents or effects currently modeled in *AMedP-7.5* includes a pre-exposure prophylaxis protection factor, the methodology retains this factor should users choose to input their own values to reflect national pre-exposure prophylaxis efficacy data. If no pre-exposure prophylaxis is modeled as a protection factor, then the pre-exposure prophylaxis parameter ($PF_{proph,Q,n}$) value of 1, associated with the default value of "None" specified in *AMedP-7.5* Table 2-2, should be used. Note that several biological agents within *AMedP-7.5* include pre-exposure prophylaxis in the form of antibiotics or vaccination, which the methodology treats separately; rather than a factor that reduces Effective Challenge, they are modeled to be 100% effective in some fraction of the population and 0% effective in the remaining fraction. If both kinds of pre-exposure prophylaxis are expected to be administered, then both a pre-exposure prophylaxis protection factor and the vaccination or antibiotics efficacy should be modeled. Otherwise, either effect of prophylaxis can be effectively

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42 U.S. Department of Energy, *DOE Standard: Specification for HEPA Filters Used by DOE Contractors*, DOE-STD-3020-97 (Springfield, VA: U.S. Department of Commerce, Technology Administration, National Technical Information Service, January 1997), 7.

43 Carl A. Curling and Lusine Danakian, *Documentation of Production: Allied Medical Publication 8 Planning Guide for the Estimation of Battle Casualties* (*Nuclear*), IDA Paper P-4008, (Alexandria, VA: Institute for Defense Analyses, March 2005), I-4.

removed from consideration by setting the protection factor to 1 or the vaccine/antibiotics efficacy to 0.

Uniform (*AMedP-7.5 Section 2.1.8 and Table 2-1*)

The uniform worn by military personnel in a unit is modeled as a challenge-modifying icon attribute only for nuclear thermal challenges, the resulting injuries from which are determined as described in *AMedP-7.5* Section 4.4.4 as a function of uniform. The default value in *AMedP-7.5* Table 2-1 is "Battledress Uniform (BDU) + T-shirt" to reflect the uniform for which data were available that would result in the most conservative casualty estimates.

CBRN Challenge and Effective CBRN Challenge (*AMedP-7.5 Section 2.1.2*)

AMedP-7.5 Table 2-2 specifies the required units for both CBRN Challenge (if using Input Scheme 1) and Effective CBRN Challenge (if using Input Scheme 2) for all challenge types in the methodology. CBRN Challenges intentionally do not account for any of the challenge-modifying icon attributes discussed above. As a result, their required units are meant to be compatible with the typical outputs of atmospheric transport and dispersion (AT&D) models. Some minor conversions (e.g., between different units of mass or radioactivity or an integration to reflect the duration of exposure) may still be required before the outputs of a particular AT&D model are in the form indicated in *AMedP-7.5* Table 2-2. However, all the conversions can be done without any scenario-specific assumptions about the attributes of the icons receiving the challenge.

In contrast, the Effective CBRN Challenge units are intended to be compatible with those of the standard toxicity estimates of human response. As specified in *AMedP-7.5* Table 2-2, the methodology requires that users input chemical agent challenge values in the typical units of mg-min/m^3 (or mg/m^3 for concentration-based effects) for inhalation challenges and mg for percutaneous liquid challenges.[44] Cutaneous and whole-body radiation challenges must be input in dose units of gray (free in air), which is consistent with how human response is commonly estimated.[45] Likewise, human response to nuclear blast effects is a function of the blast static overpressure (expressed in pounds per square inch (psi) or metric units of kPa),[46] and human response to nuclear thermal fluence is

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44 See chemical toxicity estimate units in U.S. Army Chemical School (USACMLS), *Potential Military Chemical/Biological Agents and Compounds*, FM 3-11.9/MCWP 3-37.1B/NTRP 3-11.32/AFTTP(I) 3-2.55 (Washington, DC: U.S. Government Printing Office, January 2005).

45 Anthony B. Mickelson, ed., *Medical Consequences of Radiological and Nuclear Weapons* (Falls Church, VA: Department of the Army, Office of the Surgeon General, Borden Institute, 2012).

46 Although much of the data on human response to blast effects are reported in psi (see following report), standard metric units (kPa) were chosen for the *AMedP-7.5* methodology. Donald R. Richmond and Edward G. Damon, *Primary Blast Injuries in the Open and in Foxholes*

described in terms of the percent BSA with second- or third-degree burns.[47] The units for biological agents and toxins were determined by the units described in the literature for each agent. In general, biological challenges were described in CFU (for bacterial agents) or PFU (for viral agents); a single CFU or PFU contains the number of viable organisms or virions necessary for growth in laboratory media. These measures are likely better approximations to the number of organisms or virions required to establish infection and cause injury than a measure of total (viable and nonviable) organisms or virions. Lastly, the units of biological toxins are in the commonly reported mass units (e.g., µg for botulism and mg for T-2 mycotoxin).

Default Values of Methodology Parameters (*AMedP-7.5 Table 2-14*)

AMedP-7.5 Table 2-14 specifies the default values for user-specifiable parameters related to the methodology. The default values for some of these parameters were presented at the series of SME meetings mentioned in Section 0. As documented in the proceedings of the chemical human response review meeting, the default times of 30 minutes to reach an MTF and 15 minutes at severity level 4 being sufficient to cause death and the default casualty criterion of WIA(1^{+}) were agreed to by the SMEs.[48] Although it was not discussed at the chemical human response review meeting, *AMedP-7.5* requires that the time to reach an MTF be less than 1 day because a longer time creates problems with the definitions of KIA and DOW, specifically in terms of the agent-specific flowcharts that give guidance for implementing casualty estimates.

The medical treatment flag and the day on which antibiotic treatment begins also were not briefed at the SME meetings because medical treatment had not been added to the methodology at that time. The default medical treatment flag value ("YES") is a reflection of the assumption that all available medical treatment would be provided to casualties. The default value of Day 1 for the time at which antibiotic treatment begins is consistent with a detector alarming during an attack and triggering the rapid distribution of antibiotics.

Resulting from Nuclear Type Detonations, DNA-TR-90-212 (Los Alamos, NM: Technico Southwest, Inc., for the Defense Nuclear Agency, July 1991).

47 Anthony J. Baba et al., *Incidence of Skin Burns Under Contemporary Army Uniforms Exposed to Thermal Radiation from Simulated Nuclear Fireballs*, HDL-TR-2084 (Adelphi, MD: U.S. Army Laboratory Command, Harry Diamond Laboratories, December 1986), 8.

48 Burr et al., *Chemical Human Response*.

1.4. Research Approach for the Development of Agent Models (*General Information Related to AMedP-7.5 Chapters 4 and 5*)

Although this chapter does not directly correspond to a particular section of *AMedP-7.5*, it provides important context for understanding the model development documented in Chapters 6–17 and 19–33.

Hierarchy of Source Data

The usefulness of the model parameters presented in the subsequent chapters of this paper depends heavily on both the availability of pertinent data sources and the quality of the data found therein. When raw data were available, we used them directly to define original parameters or to independently verify values calculated elsewhere. When data were limited, we identified issues and gaps and developed a strategy to generate the best possible parameter values given the constraints. This subsection describes a variety of data sources and ranks each source type according to its likelihood to lead to useful model parameters.

The literature review for each agent included a wide range of sources. Controlled human experiments conducted specifically to better understand the human response to exposure are ideal because the authors typically record the exact information required for modeling human response, such as inhaled dose and the resulting effects, which allows for dose-dependent human response models. Very little such data, however, were available for the agents considered in this paper.

For the agents considered in this paper, data from a naturally occurring outbreak or accidental exposure were sometimes available; however, the dose of agent inhaled is rarely known or even estimated. Naturally occurring cases also often involve non-inhalational exposure. Nonetheless, these accounts sometimes provide useful descriptions of the injury and its progression and can inform parts of the model.

In the absence of useful human data, controlled animal studies are typically the best sources for deriving model parameters. Non-human primate (NHP) species, due to their genetic similarity to humans, are generally viewed as the best models for human response effects, followed by non-primate mammals, and finally non-mammalian species. Yet even documented animal experimental results are sometimes difficult to find or may not supply the needed information. In this case, parameters can be derived from in vitro studies, expert opinion, or extrapolation from similar agents. As a last resort, parameters can simply be estimated. Whatever the case, the process used to arrive at each parameter is documented. Table 11 lists the various types of data sources considered, ordered by the expected relevance of the source data to developing model parameters.

Table 11. Literature Review Data Source Preferences

Data Source	Relevance of Data
Controlled Human Experiments	Highest
Human Outbreak Data (biological)	
Accidental or Intentional Human Exposures	
Controlled Animal Studies	
Primates	
Non-Primate Mammals	
Non-Mammals	
Extrapolation from Similar Agents (chemical)	
In Vitro Studies (biological)	
Expert Opinion	
Extrapolation from Similar Agents (biological)	
Best Guesses	Lowest

Chemical, Radiological, and Nuclear Agents and Effects

Chemical Agent Toxicity Parameters

For most agents, the required toxicity parameters are a median toxicity, or dosage,[49] that is expected to generate a specified effect in 50% of a population and a probit slope for each effect considered. Each set of toxicity parameters (median toxicity and probit slope) relates to a corresponding *peak* severity of symptoms, regardless of the elapsed time between challenge and the worst symptoms. Unless the supporting data for a specific agent indicate otherwise, four sets of parameter values are needed to reflect mild, moderate, severe, and very severe/lethal effects (consistent with the Injury Severity scale in Table 2). *AMedP-7.5* relates each Injury Severity Level to a specific Injury Profile and uses the toxicity parameters to estimate the number of personnel that will follow each Injury Profile.

Median toxicities and probit slopes relate to *dosage*-based effects. Although toxicity ideally should be expressed as an amount per unit mass, the assumptions of a 70 kg human and a minute volume of 15 L/min are built into reported toxicity parameter values, such that median toxicities are typically reported in units of milligram-minutes per cubic meter (mg-min/m^3), which, if multiplied by a minute volume, gives units of mass (mg) for the assumed 70 kg person. Reported toxicity parameters are also intended to be applicable to a 2-minute exposure (which is relevant for the discussion in Section 0). Probit slopes reported in this document are base 10 probit slopes, reported as probits/log (dose), as opposed to probits/ln(dose) for a base *e* probit slope.

[49] Sometimes referred to as concentration-time (Ct). The term *dosage* will be used in this document.

The qualitative labels given to toxicity parameters differ slightly from the qualitative labels used in Table 2. Table 12 provides the necessary translation between the different sets of terms.[50]

Table 12. Qualitative Labels for *AMedP-7.5* Injury Severity Levels as Compared to Qualitative Labels for Toxicity Parameters

***AMedP-7.5* Injury Severity Label**	**Toxicity Parameter Label (Associated Symbols)**
Mild	Mild ($ECt_{50\text{-mild}}$ and PS_{mild})
Moderate	Moderate ($ECt_{50\text{-moderate}}$ and $PS_{moderate}$)
Severe	Severe ($ECt_{50\text{-severe}}$ and PS_{severe})
Very Severe	Lethal (LCt_{50} and PS_{lethal})

Note: ECt_{50} = median effective dosage (concentration time), and LCt_{50} = median lethal dosage (concentration time).

Some of the chemical agents in this document also have physiological effects that are a function of *concentration*, not dosage, so probabilistic calculations based on a median toxicity and probit slope are not appropriate. Instead, concentration thresholds are used. Anyone who inhales a concentration over the threshold is modeled to exhibit certain symptoms, as indicated by the associated Injury Profile. For estimating casualties from chemicals that have both concentration and dosage-based effects, *AMedP-7.5* uses both types of Injury Profile. In this document, concentrations are given in units of milligrams per cubic meter (mg/m^3), and the relationship between dosage and concentration is that dosage can be calculated by integrating concentration over the duration of the exposure.

The ideal data source for estimating toxicity parameters and determining concentration thresholds—ethical considerations aside—is controlled human exposure under laboratory conditions. Typically, and for the five chemical agents in this paper, little such data exist. Some data on uncontrolled (accidental, suicidal, homicidal) exposure are available, but such data are, by their nature, incomplete. Typically, the dosage is not known. Toxicity studies in animals, including reporting the dosage, are relatively more plentiful.

Several difficulties arise, however, when animal model studies are used to estimate human toxicity. It is difficult to determine which animal is the best surrogate for humans in terms of toxic response and uptake of the toxin, and even the best surrogate cannot perfectly model a human. Thus, even after choosing a particular animal model, one must make assumptions to determine how to extrapolate from animal data to a human estimate.

50 Since "Very Severe" effects are lethal in the absence of medical treatment, it is not inconsistent or incorrect to relate "Very Severe" to LCt_{50}. The symbol LCt_{50} is used instead of $ECt_{50\text{-Very Severe}}$ because LCt_{50} is the symbol used in other literature.

Unfortunately, no "correct" method of extrapolation is known, so the results can vary widely. Even if a correct method were known, it is important to be aware that "[n]o single value or number adequately addresses the reality of toxic effects from exposure to a hazardous material" and that "[f]oundation data for all but a very few chemicals, is generally inadequate or unsatisfying."[51]

Where possible, we used toxicity estimates previously published by recognized experts—researchers at the Edgewood Chemical Biological Center (ECBC) and the Chemical Security Analysis Center (CSAC). Their estimates are almost exclusively based on animal data, so the aforementioned considerations apply. Further, because the available ECBC/CSAC estimates are only for lethal and severe effects, we developed our own estimates for moderate and mild effects, and these estimates are also based primarily on animal data, so the aforementioned considerations again apply. Although it was necessary to develop moderate and mild toxicity parameter value estimates for *AMedP-7.5*, we do not recommend using these estimates for any other purpose.

Using Haber's Rule to Estimate Toxicity Parameters for *AMedP-7.5* Use Only—Equivalent Prompt Dosage (EPD)

Haber's rule is an approximation that states that for gas concentration C and exposure time t, any two groupings of C and t that have equivalent mathematical products produce equivalent toxic effects (K):

$$\text{If } C_1 t_1 = C_2 t_2, \text{ then } K_1 = K_2 = K \quad (1)$$

Haber's rule is an approximation in any case in which the host eliminates the agent (the human body is able to eliminate many chemical agents). The longer the duration of exposure, the less accurate Haber's rule is thought to be. Reported toxicity parameters for the agents in this document are intended for exposures of 2-minute duration, so ideally, the toxicity parameter estimates generated as part of the analysis documented in this document must also be for 2-minute exposures (for consistency). However, much of the supporting data available for developing the chemical agent models relate to exposures of relatively long duration (even up to hours). Making use of such data requires some method of accounting for the human body's self-recovery mechanisms so that the data can be extrapolated to a 2-minute exposure.

One common method of accounting for recovery mechanisms is toxic load modeling (TLM), which is essentially a "black-box" method of accounting for the fact that the human body detoxifies itself. It incorporates the fact of detoxification in a general sense, but the

51 Douglas R. Sommerville, Stephen R. Channel, and John J. Bray, *Proposed Provisional Human Toxicity Estimates for Several Toxic Industrial Chemicals* (*TIC*), ECBC-TR-856 (APG, MD: RDECOM, November 2012), 8, ADB386113.

mathematical expression of that detoxification is entirely empirical (and also highly variable—the form used here is the simplest). We believe that a better way of accounting for self-detoxification and recovery would be to create pharmacokinetic- and biochemistry-based models that account for factors such as the rate of detoxification likely being dependent on the total agent concentration (a general principle of chemistry) and the likely time-dependence of the rate of detoxification (due to the body's up-regulating expression of detoxification proteins). However, we bow to the realities that such models do not currently exist for the agents of interest here and that there appears to be little interest in developing such models. This document will therefore continue with a discussion of TLM and how it was used in the analysis described in later chapters.

As mentioned, TLM is an empirical model. Its most basic form[52] is shown in Eq. 2, which is similar to Eq. 1, except that it raises the concentration terms to the power of n, the toxic load exponent (TLE):

$$C_1{}^n t_1 = K = C_2{}^n t_2 \qquad (2)$$

The TLE can be empirically estimated from binomial dose-response data, but the value derived is attached to the route of exposure and the specific endpoint that was measured. Thus, in theory, a TLE derived from inhalation lethality data should *not* be applied for estimating toxicity parameters for the inhalation mild endpoint, for example. Out of expedience, however, a single TLE value is often applied across different effects but within the same route of exposure.[53] For each of the chemical agents of interest for *AMedP-7.5*, only one inhalation TLE estimate is available, and in each case, it is applied across different levels of effect. The application of a TLE to a level of effect other than the one from which it was derived introduces some additional level of uncertainty to the resulting toxicity parameter estimates.

Another source of uncertainty is that TLE values are derived from laboratory experiments in which *constant* concentrations are used for the challenge. Although researchers have begun testing the effect of non-constant concentrations,[54] the applicability of TLE values derived from constant concentration data to the more realistic scenario of wildly

52 Many other forms have been suggested and used, but the form shown here is appropriate for this document because the concentration data are single values, not time varying.

53 For example, see USACMLS, *Chemical/Biological Agents and Compounds*, II-17, II-20. Note also that the same document shows a *different* value for GD inhalation mild than for GD inhalation severe/lethal (page II-23) because data were available to generate a separate estimate.

54 Lisa M. Sweeney, Douglas R. Sommerville, and Stephen R. Channel, "Impact of Non-Constant Concentration Exposure on Lethality of Inhaled Hydrogen Cyanide," *Toxicological Sciences* 138, no. 1 (2014): 205–216.

fluctuating challenge concentration is not clear. Given the current state of understanding, this uncertainty must be acknowledged but cannot be addressed in any quantitative way.

The specific way in which TLM was used in generating models for this TRM is as follows. To attempt to compensate for supporting data being for relatively long-duration exposures, we used the TLM concept to calculate an equivalent prompt dosage (EPD). The EPD is an estimate of the total dosage that, if inhaled during a 2-minute exposure,[55] would cause same physiological effects as a dosage that was inhaled over some other length of time. Rearranging Eq. 2 leads to Eq. 3, which calculates the concentration required (C_2) such that over some postulated exposure duration (t_2), the physiological effects K would be equal to those caused by a different exposure with known concentration (C_1) and exposure duration (t_1).

$$C_2 = C_1 \left(\frac{t_1}{t_2}\right)^{\frac{1}{n}} \tag{3}$$

Multiplying Eq. 3 by the postulated exposure duration t_2, and setting t_2 equal to 2 minutes gives Eq. 4, which calculates the EPD. The use of these formulae is described in the agent-specific chapters.

$$C_2 \times 2 \text{ minutes} = \text{EPD} = C_1 \left(\frac{t_1}{2 \text{ minutes}}\right)^{\frac{1}{n}} \times 2 \text{ minutes} \tag{4}$$

1. Injury Profiles

Table 13 is an example Injury Profile used for the purpose of discussing the general features of Injury Profiles. Note that (1) the only time points included in Table 13 are those for which the Injury Severity Level changes for one of the Injury Profiles, and (2) the Injury Severity Level is modeled to change as a step function. Thus, for example, the GB Mild Injury Profile indicates Injury Severity Level 1 between 15 and 150 minutes and an abrupt change to Injury Severity Level 0 at 150 minutes.

Table 13. Inhaled GB Injury Profiles

Time Point (min)	Injury Profile			
	Mild	Moderate	Severe	Very Severe
1	0	2	3	4
3	1	2	3	4
15	1	2	3	4[a]

55 In theory, the EPD formulae shown in Eq. 6 could be used to extrapolate from any exposure time to any other exposure time. We do not recommend such extrapolations. In fact, if there had been any other option, we would have entirely avoided calculating or even discussing TLM and EPD.

150	0	2	3
1000	0	2	2
1940	0	1	2
8640	0	1	1

[a] According to the default value for $T_{death\text{-}CN\text{-}SL4}$, death would be modeled at this point.

Each Injury Profile is linked to a specific set of toxicity parameters (e.g., the GB Mild Injury Profile corresponds to the $ECt_{50\text{-}mild}$ and PS_{mild}), such that the toxicity parameters can be used to estimate the number of personnel that will follow each Injury Profile. A group of personnel following the same Injury Profile is referred to as an Injury Profile cohort. For an untreated casualty estimate, *AMedP-7.5* uses the Injury Profile to determine the final outcome for each Injury Profile cohort. For a treated casualty estimate, the Injury Profile is followed until the point at which medical treatment begins, and then the medical treatment outcome reporting table (see Subsection 1.A.2) is used to determine the outcome.

Developing Injury Profiles is a difficult and somewhat subjective task that involves painstaking review of the open literature and controlled access archives, such as those at the Defense Technical Information Center (DTIC), which contain many historical records from chemical weapons research programs. For the agents in *AMedP-7.5*, the supporting data are from uncontrolled human exposures, controlled human exposures (the few for which data are available), and controlled animal exposures.

One complication with using human data to develop Injury Profiles, however, is that Injury Profiles should describe what happens if *no treatment is provided*, whereas in reality, humans almost always receive treatment. Thus, some human data are not truly relevant for the purpose of developing Injury Profiles. If they are used anyway (due to a lack of other data), then the resulting models are somewhat biased.

One final note related to Injury Profiles is that each of the chemical agent chapters contains a qualitative description of the physiological effects of the agent (Section C of each chapter), culminating in a table that links the different Injury Severity Levels with a set of associated symptoms. As was the case with similar tables reported in *AMedP-8*(*C*), the symptoms listed in those tables

> …do not necessarily represent all [physiological] systems that might be impacted by exposure to [the agent]. Rather, they represent those systems that would be expected to cause individuals to seek medical attention soonest—those that would be expected to manifest symptoms earliest and at the highest severity. There may be other symptoms of lesser medical significance or severity which are not described.[56]

[56] Curling et al., *Technical Reference Manual*, 23.

Likewise, the Injury Profiles developed in later chapters are based on the symptom sets reported at the end of Section C in each chemical agent chapter

2. Medical Treatment Outcome Reporting (MTOR) Tables

As the name suggests, MTOR tables account for two things: (1) the effects of medical treatment on casualty outcomes and (2) how casualty status is *reported*. The effects of medical treatment are incorporated into the models as probabilities of different outcomes as a function of the Injury Profile. The incorporation of the effects of medical treatment as probabilities of different outcomes depends on the supporting data—there is no default form for an MTOR. For GB, for example, Table 14 (reproduced from *AMedP-7.5*) shows the entire GB mild cohort being CONV on Day 2, whereas the GB severe cohort's time to CONV is split over two consecutive days. These differences are based on the supporting data as summarized in Section 0 of this document.

Table 14. GB Medical Treatment Outcome Reporting (from *AMedP-7.5*)

Injury Profile	DOW[a]	CONV[a]	RTD[a]
GB Mild	0%	Day 2: 100%	Day 8: 100%
GB Moderate	0%	Day 3: 100%	Day 15: 100%
GB Severe	0%	Day 4: 50% Day 5: 50%	Day 31: 100%
Self-aid/buddy aid only:			
GB Very Severe, $X^{eff}_{GB,ih}$[a] < 100	0%	Day 15: 100%	0%
GB Very Severe, $X^{eff}_{GB,ih}$[a] ≥ 100	Day 2: 100%	0%	0%
Self-aid/buddy aid + further medical treatment:			
GB Very Severe, $X^{eff}_{GB,ih}$[a] < 165	0%	Day 15: 100%	0%
GB Very Severe, $X^{eff}_{GB,ih}$[a] ≥ 165	Day 2: 100%	0%	0%

[a] $X^{eff}_{GB,ih}$ is the Effective CBRN Challenge (dosage) of inhaled GB.

As indicated by the supporting data, additional Injury Profiles may be created for an MTOR table. For example, for GB, self-aid/buddy aid *without* further medical treatment is modeled as preventing death for up to $3\times LCt_{50}$, and self-aid/buddy aid *with* further medical treatment is modeled as preventing death for up to $5\times LCt_{50}$. Thus, the Very Severe Injury Profile is split among several options, based on the treatment available and the Effective CBRN Challenge (see Table 14).

The difference between casualty *status* and casualty *reporting* is important—the main distinction being that casualties can change from one status to another on any given day, but their status can only be *reported* once per day (per the output time resolution of *AMedP-*

7.5). Thus, *AMedP-7.5* incorporates the concept of reporting a casualty's most relevant status on a given day.[57] The rules for doing so are reproduced in Table 15.

Table 15. *AMedP-7.5* Casualty Category Reporting Rules

Initial Category, Day X	Final Category, Day X	Report As, Day X	Report As, Day X + 1
WIA	KIA[a]	KIA	KIA
WIA	DOW	WIA	DOW
WIA	CONV	WIA	CONV
WIA	RTD	WIA	RTD
CONV	RTD	CONV	RTD

[a] By definition, this casualty category can only occur on Day 1.

The Table 15 rules are built into the MTOR tables derived in this TRM and are integrated as stated into *AMedP-7.5*. As an example of how the rules affect MTOR entries, the supporting data indicated that mild GB casualties would become CONV on Day 1,[58] but Table 14 does not report the casualties in the GB Mild row as CONV until Day 2, per the rule specified in the fourth row of Table 15. This approach allows the planner to allocate resources for those casualty for Day 1, since they will require medical attention for at least some portion of that day.

For nuclear casualties, the simultaneous occurrence of radiation, blast, and thermal injuries creates a complication in determining (1) the fraction of casualties moving from one casualty category to another and (2) when those casualties change categories. The same issue may arise for VX, HD, CG, CK, RDDs, and fallout casualties when $Flag_{MT}$ = Yes, because MTORs do not make use of Composite Injury Profiles. Each casualty may nevertheless be following more than one Injury Profile; in such cases, the MTOR table would therefore indicate two different outcomes that must be deconflicted.

Table 16 describes the rules for reporting casualty categories the situations described in the previous paragraph. The hierarchy for casualty categories is as follows: DOW > WIA > CONV > RTD. That is to say, if any of the Injury Profiles specify that a casualty is DOW on a given day, that is the overall categorization, regardless of the other Injury Profiles. Likewise, if individuals are modeled as WIA according to at least one Injury Profile, then they are modeled as WIA regardless of the other Injury Profile casualty categories (as long

57 For example, medical planners need to know whether a person will require medical attention on a given day. Thus, the rules are tailored around ensuring that if someone requires attention even for a fraction of that day, his/her status is reported such that a medical planner can account for the need (and translate that need into the resources required to meet it).

58 See Section 0.

as none are DOW). The only way an individual could be modeled as RTD overall would be to have all Injury Profiles specify RTD at that time.

Table 16. *AMedP-7.5* Casualty Category Reporting Rules for Multiple Injury Profiles

Injury Profile 1 Category	Injury Profile 2+ Category	Overall Reported Category
DOW	DOW/WIA/CONV/RTD	DOW
WIA	WIA/CONV/RTD	WIA
CONV	CONV/RTD	CONV
RTD	RTD	RTD

Since MTOR tables sometimes specify that individuals transition to a new casualty category over multiple days (e.g., RTD Day 2: 50%, Day 3: 50%), individuals following the same set of Injury Profiles may be split into different casualty categories and therefore be subject to different reporting rules. The following set of rules specifies the percentage of individuals in each casualty category on a given day. Although the MTOR tables report the percentage of individuals that enter a new casualty category by day, the rules for combining the MTOR rules for different Injury Profiles are described using the total number of individuals in a given casualty category on a given day (rather than just the number that entered on that day). Note that in this case, Injury Profiles are not assumed to be independent; for instance, those individuals that die according to one Injury Profile are assumed to be a subset of those that die according to another Injury Profile. This is a simplification to avoid numerous probabilistic calculations like those specified in *AMedP-7.5* Section 4.1.2.

- DOW: The overall percentage of individuals categorized as DOW is the maximum percentage categorized as DOW from all the individual Injury Profiles.
- WIA: The overall percentage of individuals categorized as WIA is the minimum of either (1) the maximum percentage categorized as WIA from the individual Injury Profiles or (2) 100% minus the overall percentage of individuals categorized as DOW.
- CONV: The overall percentage of individuals categorized as CONV is zero if either (1) the sum of the overall percentages of individuals categorized as either DOW or WIA is 100% or (2) the percentages of individuals categorized as CONV from the individual Injury Profiles are all zero. Otherwise, the overall percentage of individuals categorized as CONV is the greater of (1) the minimum nonzero percentage of individuals categorized as either CONV or RTD in any of the individual Injury Profiles or (2) 100% minus the sum of the overall percentages of individuals categorized as either DOW or WIA.

- RTD: The overall percentage of individuals categorized as RTD is 100% minus the sum of the overall percentages of individuals categorized as DOW, WIA, or CONV.

Finally, a caveat that applies to all MTORs. Similar to Injury Profiles, developing MTOR tables is difficult, somewhat subjective, and based on the information that can be found in the literature. Human data tend to be more relevant in this case than for Injury Profiles since the goal is to capture the effects of medical treatment, and most reports of human exposures involve medical treatment. As necessary, some animal data are used to fill in knowledge gaps. In some cases, injuries are sufficiently mild so that recovery occurs rapidly and independently of medical treatment. In such cases, the information reported in the MTOR is typically taken directly from the Injury Profile, although there are some cases where SMEs preferred to have casualties become CONV instead of RTD despite the Injury Profile indicating Injury Severity Level 0 at some time. In all cases, the agent-specific chapters later in this document fully explain the derivation of the MTOR table.

Biological Agents

Probit Analysis

Some of the infectivity/effectivity and lethality models presented in this TRM are derived from binomial dose-response data. Each data point is of the form (dose, number of test subjects challenged, number of test subjects responding), where the numbers of test subjects challenged and responding are used to calculate a percent response. Since the response is binomial (responding or not responding), linear regression via probit was the natural choice for the method of analysis.

The specific method used in this TRM to derive an infectivity model from the data was maximum likelihood estimation (MLE) applied to a log-probit model (hereafter referred to as *probit analysis*). This method was chosen because it is well accepted and commonly used within the toxicology and CBRN defense communities.[59]

In this TRM, probit analysis involves simultaneously estimating two parameters (using an iterative procedure): the median effective stress (μ) and the standard deviation of the effective stress (σ). The specific algorithm used for probit analysis was that described by Tallarida.[60]

Finally, the results of probit analysis are conventionally discussed in terms of median infectious dose (ID_{50}), median lethal dose (LD_{50}), or median effective dose (ED_{50})

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59 USACMLS, *Chemical/Biological Agents and Compounds*; Anno et al., *AMedP-8* (*Biological*) *Methods Report*; NATO, *AMedP-8*(*C*); Ronald J. Tallarida, *Drug Synergism and Dose-Effect Data Analysis* (Washington, DC: Chapman & Hall/CRC, 2000); "Hazard Prediction and Assessment Capability," version 5.3 (Defense Threat Reduction Agency (DTRA), 2013).

60 Ronald J. Tallarida, "Quantal Dose-Response Data: Probit and Logit Analysis," chap. 6 in *Drug Synergism and Dose-Effect Data Analysis* (Washington, DC: Chapman & Hall/CRC, 2000).

(generally referred to as the median toxicity) and probit slope (PS), rather than μ and σ; Equations 5 and 6 show the relations between the two sets of parameters.[61] Equation 7 shows how the probability of response, as a function of dose, can be estimated using the standard normal cumulative distribution function (CDF) (Φ), the PS, and the median toxicity.

$$\mu = \log_{10}(\mathrm{ID}_{50}, \mathrm{LD}_{50}, \text{or } \mathrm{ED}_{50}) \tag{5}$$

$$\sigma = \frac{1}{PS} \tag{6}$$

$$\text{Probability of response} = \Phi\left(PS \cdot \log_{10}\left(\frac{\text{dose}}{\mathrm{ID}_{50}, \mathrm{LD}_{50}, \text{or } \mathrm{ED}_{50}}\right)\right) \tag{7}$$

In several places later in this TRM, we present the results of our probit analysis of some dataset. Table 17 is an example of the inputs to the probit model for ricin, and Figure 1 shows the plotted data and curve fit resulting from the probit analysis. The final estimate from this example is an LD_{50} of 0.56 µg/kg with 95% confidence interval (CI) of 0.37 to 0.76 µg/kg, and a PS of 6.7 with 95% CI of 2.4 to 11.0.

Table 17. Example Data and Probit Results from a Ricin Inhalation Study with BALB/c Mice

Dose (µg/kg)	Number Exposed	Number Dead
0.17	6	0
0.35	6	0
0.69	6	6
1.04	5	4
1.38	6	6

Note: BALB/c mice are an albino, laboratory-bred strain of the house mouse.

61 Ibid., 97, 106; Douglas R. Sommerville et al., *Review and Assessment of Chlorine Mammalian Lethality Data and the Development of a Human Estimate R-1* (APG, MD: CSAC, June 2009), B–1.

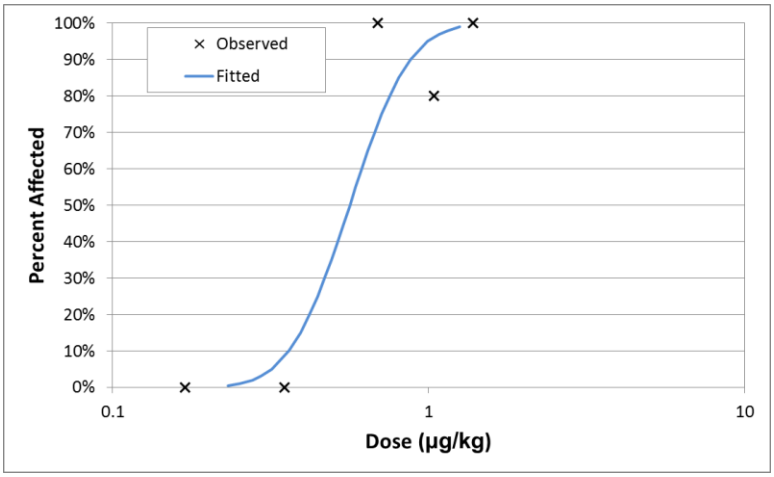

Figure 1. Example Fit to Data from a Ricin Inhalation Study with BALB/c Mice

For comparison, Benson et al.,[62] on page 250 of their paper reporting the results used for this example, reported an LD_{50} of 0.58 µg/kg with 95% CI 0.35 to 0.77 µg/kg but did not report a PS.

A final note on probit analysis is that the Tallarida algorithm we used is not designed to be used if *all* the data include a 0% or 100% response. One of the first steps of the algorithm is to calculate the percentage responding for each dose level; when the value is 0% or 100%, that data point is not used in the initial step of the iterative process. Thus, if all data points are 0% or 100%, the process cannot proceed. When we encountered datasets with all 0% or 100%, we changed 0% to 0.1% and 100% to 99.9%, which allowed the iterative process to initiate, anticipating that this would have little effect on the final answer, since the process is iterative. To check the robustness of this method, we verified that the final estimates change insignificantly if:

- Only *one* of the 0% data points and *one* of the 100% data points are changed to the other values (instead of every data point).
- A dataset with data points other than 0% and 100% response is split up into individual data points (i.e., the same dose is entered five times, each with $n = 1$, instead of being entered one time with $n = 5$).

3. Route of Exposure

Biological agent/disease model parameters may be dependent on the route of exposure. Since the context of intended use for the models is warfare, inhalation is the preferred route of exposure. However, in some cases in this document, data from natural outbreaks of disease or non-inhalation experiments are used out of necessity (because of

62 Janet M. Benson et al., "The Acute Toxicity, Tissue Distribution, and Histopathology of Inhaled Ricin in Sprague Dawley Rats and Balb/C Mice," *Inhalation Toxicology* 23, no. 5 (2011): 247–256.

the lack of other data). In these cases, it is either assumed that there is no dependence on route of exposure or that dependence is ignored. When this approach is used, it is specifically described.

For toxins, ignoring route dependence may be an especially grave mistake because the presentation of the injury is dependent on the specific tissue damaged by the toxin, which is, in turn, determined by the exposure route. For example, inhaled toxin will tend to cause more damage in the lungs, while ingested toxin will tend to cause more damage in the lower GI tract. Since the tissue damage is caused by a chemical reaction, the latent period may or may not be affected by the route of exposure.

Although replicating organisms cause injury by very different mechanisms than toxins, features of the resulting disease still may depend on the route of entry. As warranted for each agent, such possible dependencies are discussed in the Chapters 19–33.

4. Aerosolization Parameters

Aerosolization parameters, such as the particle size distribution, are critical factors in determining the delivered dose. For example, if the particles are too small, many of them will be exhaled; if they are too large, they will not penetrate as deeply into the respiratory system. The importance of this fact is explicitly discussed in some of the toxin literature.

That said, however, an inherent quality of the human response models for *AMedP-7.5* is that aerosolization parameters, such as particle size distribution, cannot be accounted for. In effect, we assume that the designs of experiments reported in the literature are sufficient to represent weaponized agents unless, for some specific reason, we believe the experiment was done poorly or in some other way that renders the data irrelevant.

The net effect on the casualty estimate depends entirely on the differences between the agent in a fielded weapon and the agent in experiments and is therefore unknown.

1.5. Chemical Agent Assumption and Constraint, Chemical Agents Toxicity Source Documents, and Transition from Threshold to Probit Model (*AMedP-7.5 Sections 4.2.1 through 4.2.13*)

Chemical Agent Assumption and Constraint (*AMedP-7.5 Section 4.2.1*)

Assumption: All individuals are 70-kilogram males.

For chemical agents, the methodology is based on toxicity data expressed in mass per kilogram and which assume exposure to a 70 kg male. A 70 kg male is consistent with the "standard man" described in the *Radiological Health Handbook*.[63] This body weight may not be typical of most military personnel, who can be significantly heavier (or lighter) than 70 kg. Being heavier may result in a less severe injury from a specified concentration time or dose, as the amount of agent is distributed in a larger mass of tissue. Conversely, being lighter than 70 kg may result in a more severe injury. Thus, this assumption may lead to either an overestimate or underestimate of the number and severity of casualties to a degree that is determined by the distribution of body weight among the population at risk.

This assumption allows direct use of the toxicity estimates taken from the sources described in Section 1.B, but note that variations in body weight will affect the amount of agent needed to cause a specified physiological response.

Constraint: The user must choose to use either Haber's rule or toxic load modeling.

Haber's rule states that the severity of toxic effects from chemical agents depends only on the total challenge, independent of the duration over which the challenge was accumulated. Toxic load modeling is an empirical attempt to account for the fact that the body has natural repair and recovery mechanisms. For those agents with a toxic load exponent greater than 1.0, the effect of toxic load modeling is that if the challenge is accumulated over a relatively long time, the human response will be less severe than if the challenge was accumulated over a relatively short time. No agents in this methodology have a toxic load exponent less than 1.0, which would imply that a challenge accumulated over a relatively long time would result in a more severe human response than if the challenge was accumulated over a relatively short time.[64] Although it is not clear which method produces a more accurate casualty estimate, having the option allows the user to generate a range of estimates by running the methodology once for each option.

The choice of whether to use Haber's rule or toxic load modeling is dependent on which model is more accurate for the realistic scenario of a time-varying concentration.

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63 U.S. Department of Health, Education, and Welfare, *Radiological Health Handbook*, 215.

64 James A. Romano, Jr., Brian J. Lukey, and Harry Salem, eds., *Chemical Warfare Agents: Chemistry, Pharmacology, Toxicology, and Therapeutics, Second Edition* (Boca Raton, FL: CRC Press, 2008), 241.

Unfortunately, the answer to this question is unknown. Little experimental validation of toxic load models for time-varying concentration has been done, and thus there is in general little basis for choosing Haber's rule or toxic load instead of the other. Haber's rule has a firmer basis in physical reality, since the toxic load model is entirely empirical, but the toxic load model does fit better with some laboratory experiments. Ideally, casualty estimates should rely on toxicity models that are based on the pharmacokinetics and biochemistry of the specific agent, but such a model does not currently exist.

It is known that Haber's rule tends to report more severe physiological effects than would really occur, and that the opposite is true of toxic load models, at least when they are applied to ensemble-averaged plumes such as those created by most AT&D models (e.g., the U.S. Hazard Prediction and Assessment Capability). Thus, if one is required to choose between the two toxicity models, being aware of each model's bias becomes the key to making a decision between the two methods. Although *AMedP-7.5* is a medical planning tool, which would tend to favor Haber's rule to guard against supply and logistics shortfalls, the models have been used for other purposes. The methodology can therefore provide multiple casualty estimates, each with an associated bias, and the user can decide how to use the results on a case-by-case basis.

B. Chemical Agent Toxicity Source Documents (*General Information Related to AMedP-7.5 Sections 4.2.2 through 4.2.13*)

1. FM 3-11.9

In 2005, the U.S. DOD published FM 3-11.9 as part of doctrine. It provides estimated toxicity parameters for a wide variety of chemical agents. Its nerve and mustard agent parameter value estimates are from the Reutter-Wade report, the Grotte-Yang report, or the early results of the Low-Level Chemical Warfare Toxicology Research Program (LLTP)[65]—human and animal data. Its estimates for other chemical agents considered in this TRM are based on human and animal data and older doctrine. Although, for the most part, it does not provide new estimates, FM 3-11.9 is the primary doctrine for estimates of the values of the chemical agent parameters presented therein.

2. *AMedP-6*(*C*), Vol. III and *AMedP-7.1*

The purpose of these documents, as stated in *AMedP-6*(*C*), is to serve "as a guide and reference for members of the military forces medical services on the recognition and management of CW agent casualties and other noxious chemical injuries" in both warfare and contingency operations.[66] *AMedP-6*(*C*) was promulgated in 2006, and its successor *AMedP-7.1* was a Final Draft and nearing promulgation during the development of this

65 See Section 1.B.6 for details on the Low-Level Toxicology Program.

66 NATO, *AMedP-6(C),* Vol. III, 1-1.

TRM. *AMedP-6*(*C*) provides only two toxicity estimates,[67] whereas *AMedP-7.1* contains a table listing toxicity estimates for many chemical agents.[68] Neither document cites sources.

3. Reutter-Wade Report

The purpose of the report was "to reconcile the many existing, disparate human toxicity estimates for several chemical agents."[69] It therefore contains "an extensive review of the relevant human and animal toxicological data, and a compilation of the more often-quoted existing human toxicity estimates, along with the data, assumptions, and rationale upon which those estimates were based (when available)."[70] It was the first large-scale effort to develop generally accepted parameter value estimates. Naturally, the report also identified data gaps, leading to the LLTP.

4. Grotte-Yang Report

The Grotte-Yang report provides a summary of the recommendations from an SME review of the Reutter-Wade report. In some cases, it recommends values that differ from the Reutter-Wade report. It concludes, "these values are the best estimates we have for these six agents, and they represent the consensus of representatives of the scientific, medical, analytical, and operational communities based on extensive examination of available data and careful review of that examination."[71]

5. USAMRICD Handbooks and *Medical Aspects of Chemical Warfare*

The purpose of the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD) Handbooks, *Field Management of Chemical Casualties Handbook* (*FMCC*) and *Medical Management of Chemical Casualties Handbook* (*MMCC*), is to "provide concise, supplemental reading material for attendees of [USAMRICD training courses]."[72] The disclaimers specifically state that they are to be used as guides and that they are not doctrine. Similarly, *Medical Aspects of Chemical Warfare* (*MACW*) describes itself as intended for military educational use, and as not doctrine.[73]

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67 Ibid., 5-5.

68 NATO, *AMedP-7.1*, 18-4 (page number is correct as of Study Draft 4).

69 Sharon A. Reutter and John V. Wade, *Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates Appropriate for Defending the Soldier* (*U*), ERDEC-SP-018 (APG, MD: ERDEC, 1994), abstract. SECRET.

70 Ibid.

71 Jeffrey H. Grotte and Lynn I. Yang, *Report on the Workshop on Chemical Agent Toxicity for Acute Effects*, IDA Document D-2176 (Alexandria, VA: IDA, 2001), 11. UNCLASSIFIED.

72 Gary Hurst et al., eds., *Field Management of Chemical Casualties Handbook*, 3rd ed. (APG, MD: USAMRICD, Chemical Casualty Care Division (CCCD), February 2007), front matter; and Gary Hurst et al., eds., *Medical Management of Chemical Casualties Handbook*, 4th ed. (APG, MD: USAMRICD, Chemical Casualty Care Division (CCCD), February 2007), front matter.

73 Shirley D. Tuorinsky, ed. *Medical Aspects of Chemical Warfare*, Textbooks of Military Medicine (Washington, DC: Office of the Surgeon General, Borden Institute, Walter Reed Army Medical Center, 2008), iix.

A relevant implication of the disclaimers is that the documents were not intended to provide up-to-date parameter value estimates—the latest DOD doctrine should instead be consulted. Indeed, it seems that most of the parameter value estimates reported in these sources are outdated. Despite the limitations, these sources were helpful for providing general guidance and, in the case of *MACW*, references that led to original data sources.

6. Low-Level Chemical Warfare Toxicology Research Program (LLTP)

The LLTP, which began in 1998, was initiated in response to the Reutter-Wade report, which identified data gaps that resulted in low-confidence parameter value estimates for low-level exposure to GB, GD, GF, and VX. The particular focus was the future development of revised defense-minded toxicity estimates. Reutter's 2007 report "Low-Level Toxicology and the Human Toxicity Estimates"[74] contains an excellent summary of the necessity of the LLTP.

The LLTP produced new data from studies in which animals were acutely exposed to a single vapor dose of an agent of interest. Analysts used the new data to develop new toxicity estimates. Although there are annual reports, we chose to use the final report as the source of toxicity estimates from the LLTP. As the final report states, the "results are scientifically auditable, transparent and focused on the military operator as the population of concern."[75] In our judgment, the LLTP results should supersede all prior parameter value estimates, where there is a difference.

7. Technical Guide 230 (TG 230)

The chemical Military Exposure Guidelines (MEGs) described in TG 230 are "intended to be used as a preventive medicine tool to identify and assess chemical occupational and environmental health (OEH) hazards faced by military personnel within the deployment environment."[76] The TG 230 models are an implementation of parameter value estimates from elsewhere. Most of the nerve and blister agent MEGs are based on extensive manipulations of the parameter value estimates from the Grotte-Yang report. The least severe nerve and blister agent MEGs and all MEGs for other chemical agent in this report are equal to exposure thresholds intended for civilians.[77] Although these approaches

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74 Sharon A. Reutter, "Low-Level Toxicology and the Human Toxicity Estimates," paper presented at the Defence Against the Effects of Chemical Hazards: Toxicology, Diagnoses and Medical Countermeasures conference, Neuilly-sur-Seine, France, 2007.

75 Sandra A. Thomson et al., *Low Level Chemical Warfare Agent Toxicology Research Program FY02- FY07 Report and Analysis*, AFRL-RH-WP-TR-2008-0093 (APG, MD: ECBC, June 2008), 3. ADB343561. UNCLASSIFIED.

76 U.S. Army Public Health Command, *Environmental Health Risk Assessment and Chemical Exposure Guidelines for Deployed Military Personnel*, TG 230 (APG, MD: U.S. Army Public Health Command (Provisional), June 2010), 1.

77 U.S. Army Public Health Command, *Methodology for Determining Chemical Exposure Guidelines for Deployed Military Personnel*, Reference Document 230 (APG, MD: U.S. Army Public Health Command (Provisional), June 2010), Tables D-3 and D-6.

make sense for application as preventive medicine tools, they also mean that the MEGs are not relevant for estimating military casualties.

8. ECBC-TR-856 and CSAC Reports

The November 2012 publication *Proposed Provisional Human Toxicity Estimates for Several Toxic Industrial Compounds* describes the results of work by the U.S. Army Edgewood Chemical Biological Center (ECBC) Research and Technology Directorate to "propose provisional human toxicity estimates for military personnel exposed to inhalation and ocular hazards while participating in military operations."[78] Due to time and funding limitations, the starting point for the development of the toxicity estimates was the literature supporting the Acute Exposure Guideline Levels (AEGLs), which are civilian exposure guidelines intended to trigger evacuation. The authors performed additional analysis to modify the numbers and ensure their results were applicable to the military population and mission. The authors also noted that the entirety of the relevant literature was not necessarily available to the researchers who developed AEGLs: "For some selected TICs, extensive toxicity data are available from government or industry sources not releasable to the public (or releasable but not generally known)."[79] Where the authors deemed it necessary, they used additional sources to inform their toxicity estimates.

The lead author of ECBC-TR-856, Douglas R. Sommerville, was also the lead author in a series of reports[80] by the Department of Homeland Security's Chemical Security Analysis Center (CSAC). The CSAC reports are another look at developing many of the same toxicity estimates as those reported in ECBC-TR-856. The primary difference is that CSAC was not constrained by starting from the literature supporting the AEGLs. The CSAC reports cover fewer agents, but do so more thoroughly. Given the publication dates and authors of the various reports, it seems that the analyses supporting the CSAC reports and ECBC-TR-856 were done concurrently by many of the same people, so it is not surprising that in most cases, the CSAC reports agree with ECBC-TR-856. However, several CSAC reports are labeled For Official Use Only (FOUO) within the United States; if FOUO information is included in a NATO document, that document must be marked NATO UNCLASSIFIED, a marking we were directed to avoid for *AMedP-7.5*. Thus, only

78 Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*, 7.

79 Ibid., 10.

80 Sommerville et al., *Review and Assessment of Chlorine*; Douglas R. Sommerville et al., *Review and Assessment of Cyanogen Chloride Mammalian Lethality Data and the Development of a Human Estimate*, CSAC 11-019 (APG, MD: CSAC, DHS, October 2011), FOUO; Douglas R. Sommerville et al., *Review and Assessment of Hydrogen Cyanide Mammalian Lethality Data and the Development of a Human Estimate* (APG, MD: CSAC, DHS, November 2011), FOUO; and Douglas R. Sommerville et al., *Review and Assessment of Phosgene Mammalian Lethality Data and the Development of a Human Estimate* (APG, MD: CSAC, DHS, November 2010), FOUO.

those CSAC sources that are not FOUO were used as sources of *AMedP-7.5* toxicity values. If a CSAC estimate was FOUO, we used an ECBC-TR-856 estimate instead.

The analytical methods used to develop the military toxicity estimates published in ECBC-TR-856 and the CSAC reports are similar to those used to develop toxicity estimates published in FM 3-11.9 and the more recent estimates from the LLTP. We view the results of these reports as the most authoritative published military toxicity estimates available for the agents discussed therein.

9. ECBC-TR-795 and ECBC-TR-1013

Both reports provide new estimates of the percutaneous toxicity of VX, based on a combination of historical human (low dose) and animal (lethal) data and a new dataset from experiments in which New Zealand white rabbits and Göttingen minipigs were dosed percutaneously. ECBC-TR-795[81] provides a new LD_{50} and a new ED_{50}, with associated probit slopes for each. ECBC-TR-1013[82] provides the same LD_{50} but with a different associated probit slope and specifically states in its abstract that its estimates supersede all previously published human toxicity estimates.

10. HPAC

HPAC is software developed by DTRA. HPAC predicts the effects of CBRN releases into the atmosphere and the resulting impact on civilian and military populations, and it is the U.S. government-approved modeling tool for these purposes. HPAC implements toxicity parameters from elsewhere, and its Material Editor contains notes on the sources of the various parameters. The notes make clear that the software's chemical agent parameter values have been updated based on the latest research, where possible. Specifically, HPAC accounts for the ECBC and CSAC reports described earlier. HPAC is under constant revision, but we are privy to neither the publication schedule nor specific details on what will change. It is possible that a new version of HPAC will have updated chemical agent toxicity estimates.

11. Timeline and Traceability of Chemical Agent Sources

Many chemical agent toxicity estimates are traceable to original data. Although the USAMRICD Handbooks, *MACW, AMedP-6*(*C*), and *AMedP-7.1* do not cite sources, HPAC cites toxicity estimates from other documents. The best modern sources for chemical agent toxicity estimates are FM 3-11.9 (which is based on Grotte-Yang and

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81 Sharon A. Reutter-Christy, Douglas R. Sommerville, and Stanley W. Hulet, *VX Studies in Support of the Contact Hazard Defense Technology Objective and Recommendations for Human Toxicity Estimates*, ECBC-TR-795 (APG, MD: ECBC, August 2010), UNCLASSIFIED.

82 Sharon A. Reutter-Christy et al., *Toxicological Studies on Selected Agents and Recommendations for Human Toxicity Estimates* (*U*), ECBC-TR-1013 (APG, MD: ECBC, May 2012), SECRET. Only UNCLASSIFIED information from the report are presented in this TRM.

Reutter-Wade), the LLTP final report, the ECBC technical reports, and the CSAC reports, all of which are based on human or animal data.

Table 18 summarizes the traceability of parameter value estimates in each source, and Figure 2 depicts the evolution of parameter value estimates over time and the dependence of doctrine and implementations on the supporting publications. As indicated by the colored shapes in the bottom portion of Figure 2, the most recent publications and drafts have converged on a set of authoritative sources for toxicity estimates. Note that although *AMedP-7.1* does not specifically cite any sources, we coordinated with the author of *AMedP-7.1* and believe the final numbers in both documents will be the same. If they are not, the *AMedP-7.5* values should supersede those in *AMedP-7.1*.

Table 18. Summary of Traceability of Sources for Chemical Agents

Source	Year	Summary of Traceability
Reutter-Wade	1994	Human and animal data
Grotte-Yang	2001	Reutter-Wade, with SME modifications
FM 3-11.9	2005	Nerve and blister agents: Grotte-Yang Blood and choking agents: human and animal data
AMedP-6(*C*)	2006	No references to other sources
USAMRICD Handbooks	2007	No references to other sources
MACW	2008	No references to other sources
LLTP Final Report	2008	Modern animal data
TG 230	2010	Grotte-Yang, human and animal data
CSAC	2009–2011	Human and animal data
ECBC-TRs	2010–2012	Human and animal data
AMedP-8(*C*)	2011	IDA D-4082
HPAC	2013	FM 3-11.9, the LLTP, ECBC-TRs, and CSAC
AMedP-7.1	2017?	No references to other sources

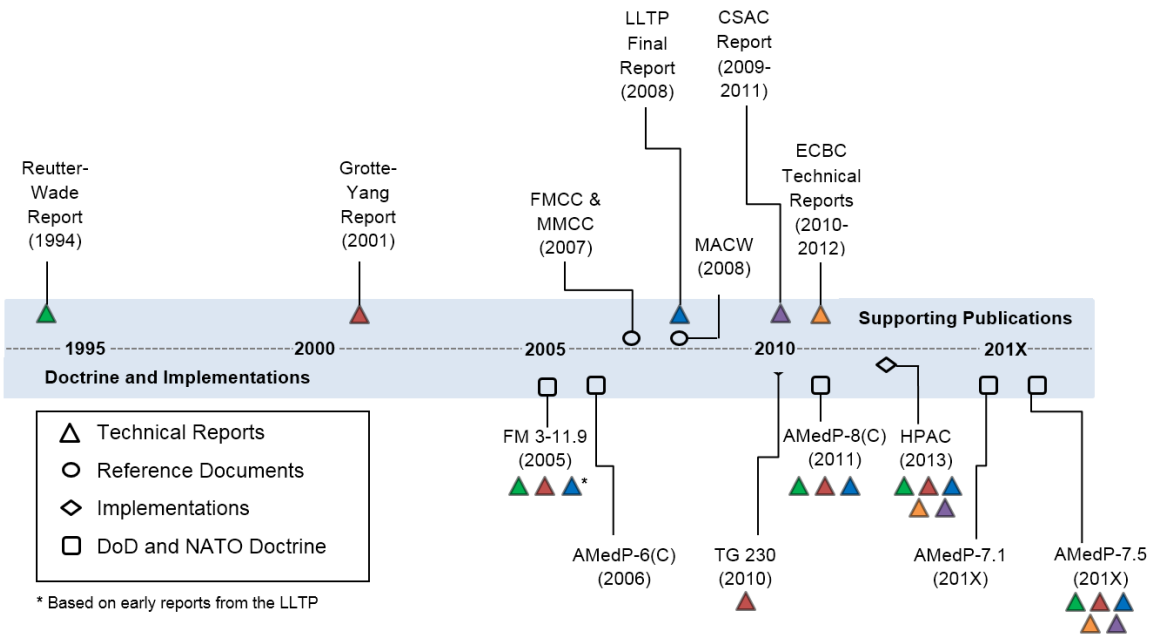

Figure 2. Source Timeline for Chemical Agent Parameter Value Estimates

Transition from *AMedP-8*(*C*) Threshold Model to *AMedP-7.5* Probit Model (*General Information Related to AMedP-7.5 Sections 4.2.2 through 4.2.13*)

In *AMedP-8*(*C*), the assignment of chemical agent Injury Profiles was a deterministic function of the Effective CBRN Challenge. Each Injury Profile was associated with a range of challenge values, and the human response for all individuals in a given range was specified by the same Injury Profile. To better capture the variability in human response among individuals with the same challenge value, the *AMedP-7.5* methodology uses a probit model to determine which Injury Profile describes an individual's human response. This section will describe the transition from the *AMedP-8*(*C*) deterministic assignment of chemical agent Injury Profiles to the *AMedP-7.5* probabilistic probit-based assignment of individuals into Injury Profiles. Note that due to a paucity of data from which to develop probit models, concentration-based effects (for CG and CK) are treated deterministically, and individuals are assigned to an Injury Profile based solely on their peak concentration values.

The fundamental idea in the *AMedP-7.5* methodology is that separate probit models for each of the four Injury Severity Levels (mild, moderate, severe, and very severe) are used to determine which Injury Profile individuals follow. Based on an individual's challenge, each probit model estimates the probability of the individual experiencing symptoms at least as severe as the associated Injury Severity Level. Consider a group of individuals all challenged with the same amount of chemical agent. Using the mild probit model, some fraction of those individuals would be estimated to have symptoms of at least mild severity. A subset of those individuals experiencing mild symptoms would also have moderate symptoms, and a subset of those individuals would have severe or very severe symptoms. The number of individuals estimated to experience mild symptoms (but not symptoms of any greater severity) would be associated with the Injury Profile(s) that peak at injury severity 1 (mild) symptoms. Likewise, disjoint subsets of individuals would be associated with moderate, severe, and very severe Injury Profiles. Because this is a probabilistic part of the model, individuals are not tracked; in effect, fractions of each individual are "assigned" to each Injury Profile, and the fractions are summed to determine the total number of individuals in the scenario following each Injury Profile.

There were a number of challenges with converting from the *AMedP-8*(*C*) methodology to the *AMedP-7.5* methodology described above. First, for effects levels not studied directly in experiments (e.g., moderate symptoms), probit model parameter values needed to be estimated to assign individuals to the corresponding Injury Profiles. Second, when multiple *AMedP-8*(*C*) Injury Profiles peaked at the same symptom severity level, a process was needed to determine how many people were assigned to each Injury Profile. Last, care needed to be taken to avoid double counting individuals as following more than one Injury Profile.

To address the first challenge, when probit model parameter values were not available in the literature for a particular severity level, we estimated those values from the parameter values associated with other effects levels. Typically, the probit slope was assumed to be equal to that of another effect level if the mechanism of injury for the two types of effects was similar. Given a probit slope value, the ECt_{50} was calculated by assuming the ECt_{16} was equal to the lower bound of the challenge range associated with the *AMedP-8*(*C*) Injury Profile that peaked at the severity level of interest. The ECt_{16} (rather than the ECt_{01}, for example) was chosen as the value for the lower bound of the *AMedP-8*(*C*) challenge range because those ranges were meant to capture the response of the "typical" individual. Reasoning that the typical individual would fall within one standard deviation of the mean of the underlying normal distribution (the middle 68%), the ECt_{16} was chosen as it represents one standard deviation below that mean.

To address the issue of how to assign individuals to one of multiple Injury Profiles peaking at the same level, we used one of two approaches. When there was no operationally significant difference between Injury Profiles—meaning no difference in how casualties would be reported by *AMedP-7.5*, particularly in reference to the 1-day reporting resolution—they were combined into one Injury Profile. If the profiles resulted in operationally distinct outcomes, then the original *AMedP-8*(*C*) challenge range boundary was used to determine which profile individuals followed. Individuals receiving challenges above the challenge boundary were assigned to the Injury Profile originally corresponding to the higher challenge range (associated with the Injury Profile with a quicker symptom severity escalation or longer duration of symptoms). Individuals with challenges below the boundary were assigned to the Injury Profile associated with the lower *AMedP-8*(*C*) challenge range.

The last challenge was to ensure that individuals were not double counted by neglecting the fact that individuals experiencing symptoms of a certain severity level are a subset of the individuals experiencing less severe symptoms. The next section describes the mathematical implementation that ensures the correct number of individuals are assigned to each Injury Profile based on the four separate probit models.

Assignment of Personnel to Injury Profiles (*AMedP-7.5 Section 4.1.2*)

AMedP-7.5 Equations 4-5 through 4-14 are used to ensure that casualties are correctly allocated to the appropriate Injury Profiles without double-counting. These equations imply that different challenge types and effects are assumed to be independent of each other. To demonstrate the concept more intuitively, consider the generic scenario illustrated in Figure 3 with two independent effects. If the probability of becoming a casualty based on Effect 1 is 0.7 and the probability of becoming a casualty based Effect 2 is 0.3, then the probability of becoming a casualty from both effects is the product of the two ($0.7 \times 0.3 = 0.21$). *AMedP-7.5* Equation 4-5 simply describes this calculation generically using the

AMedP-7.5 notation. The probability of becoming a casualty from only one effect is simply the difference between the individual probability and the joint probability (Effect 1 only: 0.7 – 0.21 = 0.49; Effect 2 only: 0.3 – 0.21 = 0.09). These calculations are described mathematically in *AMedP-7.5* Equations 4-5 and 4-6. *AMedP-7.5* Equations 4-8 through 4-14 generalize the same process just described to three different types of effects.

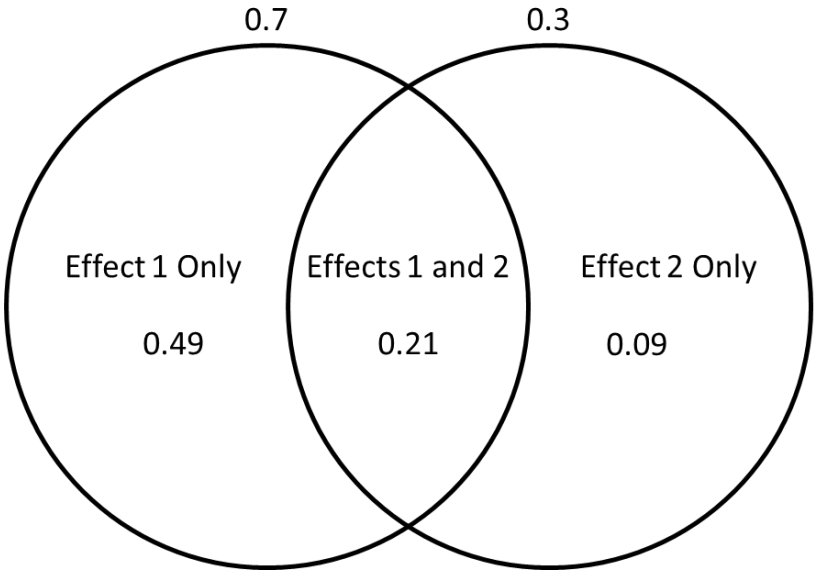

Figure 3. Example of Independently Calculated Effects

For a more concrete example, see the illustrative example in *AMedP-7.5* Annex A (Section A.4.3) of a notional attack with the chemical agent CK. In that case, individuals could be casualties as a result of their CK dosage alone, their peak CK concentration alone, or a combination of the two.

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1.6. Nerve Agent Models (GA, GB, GD, GF, VX) (*AMedP-7.5 Sections 4.2.2 to 4.2.6*)

Introduction

Chemical nerve agents are among the most toxic chemical substances known; in both vapor and liquid form, exposure can result in near-instantaneous symptoms and, at high enough doses, death. The objective of this chapter is to describe the human response models for the nerve agents GA, GB, GD, GF, and VX as they have been incorporated into *AMedP-7.5*.

The first section describes the agent-specific assumptions made in *AMedP-7.5*. Next, the chapter describes the physiological effects of nerve agents. The next section discusses the four steps taken to develop the nerve agent Injury Profiles for *AMedP-7.5*: (1) match the symptoms within each physiological system to the defined Injury Severity Levels; (2) develop the symptom progressions used in *AMedP-8*(*C*), which are tables of the Injury Severity Level over time corresponding to each physiological system; (3) combine the symptom progressions to generate the *AMedP-8*(*C*) Injury Profiles; and (4) map the *AMedP-8*(*C*) Injury Profiles to the *AMedP-7.5* Injury Profiles. The following section lists the toxicity values found in the literature for each of the five nerve agents, which are used in *AMedP-7.5* to determine the probabilistically derived proportions of individuals in each Injury Profile category. Last, medical treatment models for nerve agents are discussed.

Assumptions and Limitations (*AMedP-7.5 Sections 4.2.2.2, 4.2.3.2, 4.2.4.2, 4.2.5.2, and 4.2.6.2*)

Assumption: Percutaneous exposure to GA vapor is negligible.

Assumption: Percutaneous exposure to GB vapor and liquid are negligible.

Assumption: Percutaneous exposure to GD vapor is negligible.

Assumption: Percutaneous exposure to GF vapor is negligible.

The percutaneous vapor concentration times required to affect human response are one to several orders of magnitude greater than the inhalation concentration times required to produce similar effects.[83] Further, the liquid resulting from a GB attack, and thus the percutaneous liquid contribution to dose, may be neglected due to the agent's high volatility.[84]

Limitation: Percutaneous exposure to GA liquid is not included; note, however, that the GA percutaneous liquid threat is not negligible.

Limitation: Percutaneous exposure to GD liquid is not included; note, however, that the GD percutaneous liquid threat is not negligible.

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83 USACMLS, *Chemical/Biological Agents and Compounds*, II-17, II-20, II-23, and II-26.

84 Ibid, II-18.

Limitation: Percutaneous exposure to GF liquid is not included; note, however, that the GF percutaneous liquid threat is not negligible.

The volatilities of these agents (at 25 °C) are one to two orders of magnitude lower than that of GB,[85] and simple HPAC simulations confirm that as a result, there *would* be significant areas in which injury-producing doses of liquid would occur. Thus, ideally, percutaneous liquid exposure should be considered in *AMedP-7.5*, but data and time limitations prevented the development of the Injury Profiles that would be needed. Thus, the lack of accounting for effects of liquid doses is identified as a limitation.

Assumption: Human response due to inhaled VX vapor and percutaneous VX liquid are independent of one another—the effects of each challenge type are modeled separately and only combined in the form of a Composite Injury Profile.

Inhaled VX vapor induces human response in several physiological systems nearly instantaneously, including the ocular and respiratory systems. Human response resulting from percutaneous VX liquid takes longer to manifest and affects physiological systems differently. Thus, dosage and dose due to the two routes of exposure are represented by two separate Injury Profiles that are combined to generate a final composite VX Injury Profile, as described later in this document. It is possible that the interaction of human response resulting from exposure to inhaled VX vapor and percutaneous VX liquid may be synergistic; therefore, the assumption of the independence of human response given two routes of exposure may result in an underestimate of the number and severity of casualties.

Limitation: Percutaneous exposure to VX vapour is not included; note, however, that the VX percutaneous vapour threat is not negligible.

Although the estimated LCt_{50} for percutaneous vapor is an order of magnitude higher than the LCt_{50} for inhaled VX vapor, the difference between the severe Ect_{50}s for percutaneous and inhaled VX vapor is substantially smaller. Thus, it is incorrect to argue that the contribution of percutaneous vapor-based dose to the overall dose will be negligible relative to the inhalation and percutaneous liquid doses. However, that reasoning was used in the development of *AMedP-8*(*C*),[86] and the problem was not discovered until very late in the development of *AMedP-7.5*, at which point there was no time to develop new Injury Profiles for percutaneous VX vapor or include it in some other way.

Physiological Effects (*AMedP-7.5 Tables 4-1, 4-4, 4-7, 4-10, 4-13, and 4-15*)

The nerve agents modeled in the *AMedP-7.5* methodology act through similar mechanisms of action—all inhibit acetylcholinesterase reactions by binding at the enzyme

85 Ibid. II-15, II-21, and II-24.

86 Burr et al., *Chemical Human Response*, 10.

receptor sites and blocking hydrolysis—but they differ in other respects. Because of its high volatility, for example, GB is a nonpersistent agent and evaporates quickly. As a result, GB vapor poses an inhalation hazard but a more limited percutaneous hazard. In contrast, as a more persistent agent, VX may pose a threat in the vicinity of an attack for longer periods of time. Because of the similarities in the mechanism of action and the resulting effects, all nerve agents produce similar signs and symptoms, although the rate and severity of effect in relation to dose varies for each agent.

Nerve agents cause disease by inhibiting the proper functioning of the enzyme acetylcholinesterase in its interaction with acetylcholine. In simple terms, acetylcholine passes messages to the skeletal muscles and through the nervous system, thereby stimulating the system's reaction. Acetylcholinesterase breaks down (or hydrolyzes) the acetylcholine, ending the stimulation trigger and allowing the muscle to relax. Nerve agents inhibit acetylcholinesterase function by binding to the enzyme's receptor sites, prohibiting the acetylcholine compounds from binding to these now-occupied sites. As a result, the enzyme is unable to hydrolyze the acetylcholine, precluding the termination of the nerve signal. Because the stimulation trigger remains, and even intensifies, as acetylcholine builds up in the system, the muscles remain constantly stimulated and prevented from relaxing. This effect can eventually lead to death via several routes, including the failure of the central nervous system to stimulate respiratory drive, muscle fatigue leading to flaccid paralysis of the diaphragm, and asphyxiation due to constriction of the bronchial tubes combined with excessive secretions in the air passages. A brief summary of signs and symptoms follows to provide background material. More detailed discussions of these signs and symptoms are available in *MACW*[87] and McDonough.[88]

In addition to the respiratory system, the eyes, nose, mouth, pulmonary tract, gastrointestinal tract, skin and sweat glands, muscular system, cardiovascular system, and central nervous system can also be affected.[89] The severity of these effects is a function of dose or dosage: "The magnitude and duration of a particular physiological effect is highly dependent upon the level of agent exposure or dose of the drug."[90]

Ocular effects are usually the first symptoms, because these occur at very low exposure levels. Ocular effects include miosis (constriction of the pupil), conjunctival

87 Frederick R. Sidell, Jonathan Newmark, and John H. McDonough, "Nerve Agents," chap. 5 in *Medical Aspects of Chemical Warfare*, ed. Shirley D. Tuorinsky, Textbooks of Military Medicine (Washington, DC: Office of the Surgeon General, Borden Institute, Walter Reed Army Medical Center, 2008).

88 John H. McDonough, "Performance Impacts of Nerve Agents and Their Pharmacological Countermeasures," *Military Psychology* 14, no. 2 (2002): 93–119.

89 Sidell, Newmark, and McDonough, "Nerve Agents," 170.

90 McDonough, "Performance Impacts of Nerve Agents," 97.

injection (bloodshot eyes), eye pain, and dim or blurred vision. The duration and severity of these effects depends on the exposure dose.[91]

In addition to ocular effects, nerve agent exposure causes an increased level of secretions from the nose and the sweat and salivary glands, as well as in the pulmonary and gastrointestinal systems. In the gastrointestinal tract, these may be accompanied by abdominal cramps; nausea; vomiting; and, in smaller segments of the population, diarrhea.[92]

In the pulmonary tract, complaints may include cough, "tight chest," and shortness of breath. As the dose increases, "respiration rapidly becomes gasping and irregular, and the victim can become cyanotic and totally apneic in a severe poisoning."[93] Individuals exposed to low doses may begin to feel better shortly after moving to cleaner air environments and their respiratory complaints may resolve themselves without medical interventions. At higher doses, medical interventions are required to reduce the effects and possibly aid in ventilation.[94]

In the muscular system, the initial effects manifest as twitches, jerks, and fasciculations (visible contractions of small numbers of muscle fibers), resulting in muscle fatigue. Larger doses may result in seizures or larger muscle group contractions, causing flailing limbs or rigid hyperextension of the limbs or torso.

Psychological effects may also be present following nerve agent exposure; these may be of short or prolonged duration, depending on dose. Symptoms may include increased anxiety, tension, weakness, fatigue, forgetfulness, and irritability.

Injury Profiles (*AMedP-7.5 Tables 4-2, 4-5, 4-8, 4-11, 4-14, and 4-16*)

The basic concept of the *AMedP-7.5* methodology is that an individual is considered a casualty at the time of first onset of a specified Injury Severity Level, based on specific symptoms resulting from exposure to the causative agent. The human response component of this methodology specifies an Injury Profile depicting Injury Severity Level over time that is used to determine whether an individual is declared KIA, WIA, or DOW and thereby considered to be a casualty and, if so, at what point this would occur. The Injury Profiles for chemical agents included in *AMedP-8*(*C*) were derived from symptom progressions, which show the severity level of symptoms in the system in which they manifest (as opposed to the causative system) over time.[95] The severity level of the Injury Profile at any

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91 Ibid., 98–99.

92 Ibid., 99–100; and Sidell, Newmark, and McDonough, "Nerve Agents," 170.

93 McDonough, "Performance Impacts of Nerve Agents," 100.

94 Ibid.; and Sidell, Newmark, and McDonough, "Nerve Agents," 173.

95 Injury Profiles for chemical agents incorporated into the methodology after the publication of *AMedP-8*(*C*) were derived for the whole body rather than the underlying physiological systems. Therefore, no symptom progressions were created for these agents.

given time point corresponded to the worst severity level experienced in any of the representative physiological systems at that time. The following sections explain the historical development of the Injury Profiles in Table 31 and Table 32.

Severity Levels

As mentioned in Chapter 1, the *AMedP-8*(*C*) chemical agent methodology built on the DNA Improved Casualty Estimation (DICE) methodology for estimating human performance. For GB and VX, the DICE methodology employed six sets of signs, symptoms, and systems to represent the inhaled chemical nerve agent injury progression: upper gastrointestinal, lower gastrointestinal, respiratory, ocular, muscular, and mental. These symptoms were represented on a severity scale of 1–5.[96]

During the development of *AMedP-8*(*C*), in an effort to ensure clarity and consistency, the symptoms and systems for the chemical nerve agents were correlated to six representative physiological systems—upper gastrointestinal, lower gastrointestinal, respiratory, ocular, muscular, and neurological—in which symptoms would be expected to manifest following inhalation exposure to chemical agents. The same six systems were used to derive symptom progressions and Injury Profiles resulting from exposure to percutaneous liquid VX.

The DICE human response methodology correlated the severity levels for each of the six physiological systems to anticipated signs and symptoms; the severity levels were independent for each physiological system.[97] For example, an ocular severity of 4 (described as "temporary blindness") while operationally challenging, was not, however, equivalent to a respiratory severity of 4 ("breathing stops completely"), which could potentially kill an individual.

In contrast, symptoms in the *AMedP-8*(*C*) methodology were expressed on a single scale of 0–4, with 0 representing no observable injury and 4 representing very severe effects *independent of the physiological system*. To align the severities across the physiological systems and be able to construct useful Injury Profiles, the authors of *AMedP-8*(*C*) adjusted the severity levels associated with each set of signs and symptoms. As a result, all six physiological systems begin with a "no observable injury" level, but each system has only the number of severity levels necessary to achieve the maximum severity at which signs and symptoms for that physiological system occur. For example, if a given physiological system was not expected to manifest symptoms greater in severity

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96 George H. Anno et al., *Predicted Performance on Infantry and Artillery Personnel Following Acute Radiation or Chemical Agent Exposure,* DNA-TR-93-174 (Washington, DC: Defense Nuclear Agency, November 1994), 8–13; Gene E. McClellan, George H. Anno, and Leigh N. Matheson, *Consequence Analytic Tools for NBC Operations Volume 3: Chemical Agent Exposure and Casualty Estimation*, DSWA-TR-97-61-V3 (Alexandria, VA: Defense Special Weapons Agency, 1998), 11–16; and Deverill and Metz, *DICE Chemical Insult Program*, 15–40.

97 These correlations are derived from those completed as part of the DICE methodology.

than level 3, then the scale for that system would range from 0 to 3. Moreover, the new severity levels are aligned so that, for instance, an Injury Severity Level 3 ocular injury consists of signs and symptoms of equal operational impact to those found in Injury Severity Level 3 for the respiratory system and Injury Severity Level 3 for the muscular system. Again, these signs and symptoms are shown in the physiological system in which they manifest, rather than in the causative system.

Table 19 shows the symptom–severity level correlations created for GB and VX for use in the *AMedP-8*(*C*) methodology. Because all nerve agents included in *AMedP-7.5* are represented by the same six physiological systems, the severity levels described apply for all nerve agents.

Table 19. Nerve Agent Symptoms Severity Levels

Severity	Upper Gastrointestinal	Lower Gastrointestinal	Muscular
0	No observable injury	No observable injury	No observable injury
1	Upset stomach and nausea; watering mouth and frequent swallowing to avoid vomiting	Abdominal pain or cramps; occasional diarrhea and uncomfortable urge to defecate	Muscle twitching/ fasciculation; fatigue and weakness
2	Episodes of vomiting, possibly including dry heaves; severe nausea and possibility of continued vomiting	Frequent diarrhea and cramps; continuing defecation	Muscle trembling; lack of coordination; increased fatigue and weakness
3		Uncontrollable diarrhea and urination; painful cramps	Severe generalized twitching with or without convulsions
4			Flaccid paralysis

Table 19. Nerve Agent Symptoms Severity Levels (continued)

Severity	Ocular	Respiratory	Neurological
0	No observable injury	No observable injury	No observable injury
1	Slightly blurred, dim (may be due to tearing), or possibly irritated (conjunctival erythema and/or edema) vision	Mild shortness of breath; tight chest, coughing, and runny nose	Feelings of anxiety, irritability or euphoria
2	Blurred vision due to dimming or difficulty opening eyes; eyes sensitive to light or puffy; potential for pressure behind the eyes, eye pain, or heavy tearing	Frank shortness of breath; difficult to breathe, wheezing breath, respiratory congestion, bronchorrhea	Difficulty in concentration
3	Functional blindness (possibly accompanied by extreme headache)	Breathing sporadically stops and starts, skin has a	Aphasia; memory loss; disorientation

	purple or blue color, hemoptysis	
4	Breathing stops completely or struggling to breathe; prostration	Unconsciousness

Symptom Progressions

Using the new severity level scales, we adapted existing descriptions from the DICE methodology of symptom severity level changes over time for inhaled GB and VX for each of the six physiological systems described above. The resulting six symptom progressions (common to all nerve agents modeled) represented clinically differentiable human responses to nerve agent exposure. In 2008, SMEs at an international chemical agent human response meeting in Munich, Germany, reviewed these symptom progressions and agreed on the final versions to be included in *AMedP-8*(*C*).[98] Table 20 through Table 25 present the symptom progressions by clinical presentation for inhaled nerve agents. The "no observable injury" symptom progressions are not shown; all severity levels for those symptom progressions would be 0 for the duration of time observed. Although these different presentations were originally linked to concentration-time ranges, that information is excluded here because *AMedP-7.5* uses only the clinical presentations. As a result, they are labeled below on an arbitrary scale as "Presentation 1" through "Presentation 6," with higher numbers representing worse clinical presentations.

98 Burr et al., *Chemical Human Response*.

Table 20. Nerve Agent Inhaled Vapor Symptom Progressions by Physiological System Developed for *AMedP-8*(*C*) for Clinical Presentation 1

Time Point (min)	Upper GI	Lower GI	Muscular	Ocular	Respiratory	Neurological
1	0	0	0	0	0	0
3	0	0	0	1	1	0
150	0	0	0	0	0	0

Table 21. Nerve Agent Inhaled Vapor Symptom Progressions by Physiological System Developed for *AMedP-8*(*C*) for Clinical Presentation 2

Time Point (min)	Upper GI	Lower GI	Muscular	Ocular	Respiratory	Neurological
1	0	0	0	2	1	0
100	0	0	0	2	0	0
1000	0	0	0	1	0	0

Table 22. Nerve Agent Inhaled Vapor Symptom Progressions by Physiological System Developed for *AMedP-8*(*C*) for Clinical Presentation 3

Time Point (min)	Upper GI	Lower GI	Muscular	Ocular	Respiratory	Neurological
1	1	0	0	2	1	1
10	2	0	0	2	1	2
60	1	0	0	2	1	2
1000	0	0	0	2	1	2
2880	0	0	0	1	0	1

Table 23. Nerve Agent Inhaled Vapor Symptom Progressions by Physiological System Developed for *AMedP-8*(*C*) for Clinical Presentation 4

Time Point (min)	Upper GI	Lower GI	Muscular	Ocular	Respiratory	Neurological
1	1	1	3	3	3	3
5	2	1	3	3	3	3
15	2	2	3	3	2	3
60	1	2	2	3	2	2
100	1	1	2	3	1	2
360	1	1	1	3	1	2
1000	1	0	1	2	0	2
1440	0	0	1	2	0	2
8640	0	0	1	1	0	1

Table 24. Nerve Agent Inhaled Vapor Symptom Progressions by Physiological System Developed for *AMedP-8*(*C*) for Clinical Presentation 5

Time Point (min)	Upper GI	Lower GI	Muscular	Ocular	Respiratory	Neurological
1	2	1	3	3	3	3
3	2	1	3	3	3	4
15	2	2	3	3	3	3
30	2	2	3	3	2	3
60	2	2	2	3	2	3
100	1	1	2	3	2	3
180	1	1	2	3	2	2
240	1	1	2	3	1	2
360	1	1	1	3	1	2
1000	0	0	1	2	1	2
1440	0	0	1	2	0	2
8640	0	0	1	1	0	2

Table 25. Nerve Agent Inhaled Vapor Symptom Progressions by Physiological System Developed for *AMedP-8*(*C*) for Clinical Presentation 6

Time Point (min)	Upper GI	Lower GI	Muscular	Ocular	Respiratory	Neurological
1	2	1	4	3	4	4
15[a]	2	2	4	3	4	4

[a] Due to the high severity of symptoms, casualties are estimated to die at this point.

Note that in the case of the most severe clinical presentation for inhaled nerve agent, SMEs estimated that "very severe" effects manifested simultaneously in the respiratory, muscular, and neurological systems would result in rapid lethality (15 minutes or less). Therefore, the symptom progression for this clinical presentation is not shown beyond 15 minutes.

Table 26 through Table 28 present the symptom progressions by clinical presentation developed for percutaneous liquid nerve agent.

Table 26. Nerve Agent Percutaneous Liquid Symptom Progressions by Physiological System Developed for *AMedP-8*(*C*) for Clinical Presentation 1

Time Point (min)	Upper GI	Lower GI	Muscular	Ocular	Respiratory	Neurological
1	0	0	0	0	0	0
10	0	0	1	0	0	0
240	1	0	1	0	1	0
360	2	0	1	0	1	0
1000	1	0	1	0	1	0
1440	0	0	0	0	0	0

Table 27. Nerve Agent Percutaneous Liquid Symptom Progressions by Physiological System Developed for *AMedP-8*(*C*) for Clinical Presentation 2

Time Point (min)	Upper GI	Lower GI	Muscular	Ocular	Respiratory	Neurological
1	0	0	0	0	0	0
8	0	0	1	0	0	0
60	0	0	1	0	0	1
100	1	0	2	0	1	1
150	1	0	3	0	1	1
180	2	1	3	0	1	2
240	2	1	3	1	2	2
1440	1	1	3	1	1	2
2400	0	1	1	1	0	2
2880	0	1	0	0	0	2
5000	0	0	0	0	0	2

Table 28. Nerve Agent Percutaneous Liquid Symptom Progressions by Physiological System Developed for *AMedP-8*(*C*) for Clinical Presentation 3

Time Point (min)	Upper GI	Lower GI	Muscular	Ocular	Respiratory	Neurological
1	0	0	0	0	0	0
8	0	0	1	0	0	0
24	1	1	1	0	1	1
30	2	2	2	1	2	2
36	2	2	3	2	3	4
51[a]	2	2	3	2	3	4
60	2	2	4	2	4	4
1440	2	1	4	2	4	4
2400	1	0	4	2	4	4
2880	0	0	4	1	4	4
4320	0	0	4	0	4	4

[a] Due to the high severity of symptoms, casualties are estimated to die at this point.

AMedP-8(*C*) Injury Profiles

The symptom progressions provide the foundation for the Injury Profile, which illustrates the effect of the injury on the body overall by tracking the highest severity level across the six physiological systems at any moment in time. The six nerve agent inhaled vapor Injury Profiles and three nerve agent percutaneous liquid Injury Profiles, which were developed for *AMedP-8*(*C*), are shown in Table 29 and Table 30, respectively.

Table 29. Nerve Agent Inhaled Vapor Injury Profile Developed for *AMedP-8*(*C*) for Clinical Presentation 1

	Clinical Presentation…					
Time Point (min)	1	2	3	4	5	6
1	0	2	2	3	3	4
3	1	2	2	3	4	4[a]
15	1	2	2	3	3	
150	0	2	2	3	3	
1000	0	1	2	2	2	
2880	0	1	1	2	2	
8640	0	1	1	1	2	

[a] Due to the high severity of symptoms, casualties are estimated to die at this point.

Table 30. Nerve Agent Percutaneous Liquid Injury Profile Developed for *AMedP-8*(*C*) for Clinical Presentation 3

Time Point (min)	Clinical Presentation…		
	1	2	3
1	0	0	0
8	0	1	1
10	1	1	1
30	1	1	2
36	1	1	4
51	1	1	4[a]
100	1	2	
150	1	3	
360	2	3	
1000	1	3	
1440	0	3	
2440	0	2	

[a] Due to the high severity of symptoms, casualties are estimated to die at this point.

AMedP-7.5 Injury Profiles

When used in *AMedP-8*(*C*), each of the Injury Profiles shown in Table 29 and Table 30 was associated with a specific range of concentration times or doses. In *AMedP-8*(*C*), all individuals with a given challenge were modeled to have the same response, which was described by the Injury Profile corresponding to the range spanning that challenge value. To allow for a more realistic estimate of the total number of casualties, the deterministic dose/concentration-time-based assignment of Injury Profiles from *AMedP-8*(*C*) was replaced in *AMedP-7.5* with a probabilistic probit-based assignment of individuals into Injury Profiles.

Rather than basing the Injury Profiles on challenge ranges, Injury Profiles in *AMedP-7.5* are specific to their maximum Injury Severity Level (mild, moderate, severe, or very severe). An Injury Profile for each injury severity was developed by combining the nerve agent Injury Profiles used in *AMedP-8*(*C*). For inhaled nerve agents, the *AMedP-7.5* mild Injury Profile is simply the *AMedP-8*(*C*) Injury Profile for clinical presentation 1 shown in Table 29 (originally developed to correspond to 0.2–<1 mg-min/m^3 inhaled GB).

The *AMedP-7.5* nerve agent inhaled vapor moderate Injury Profile was formed by combining the *AMedP-8*(*C*) Injury Profiles for clinical presentations 2 and 3 from Table 29 (originally developed to correspond to 1–<6.5 and 6.5–<12 mg-min/m^3 inhaled GB, respectively). Operationally, there was no difference between the two Injury Profiles: in both cases, symptoms immediately reached severity level 2 and there is no estimated time to severity level 0. The only difference between the two profiles was the time at which the

severity level progressed from 2 to 1. For clinical presentations 2, the time was 1000 minutes (Day 1); for clinical presentations 3, the time was 2880 minutes (Day 3). Since the change from severity level 2 to 1 is *operationally* meaningless, there was no need to retain the distinct profiles. The new combined Injury Profile will drop to severity level 1 at 1940 minutes (the average of the times from the two Injury Profiles), meaning a bed may be required for Days 1 and 2, but will no longer be needed on Day 3.

The *AMedP-7.5* nerve agent inhaled vapor severe Injury Profile is the same as the *AMedP-8*(*C*) Injury Profile for clinical presentation 4 from Table 29 (originally developed to correspond to 12–<25 mg-min/m^3 inhaled GB), which was the only Injury Profile that peaked at severity level 3. The Injury Profile for clinical presentation 5 from Table 29 (originally developed to correspond to 25–<30 mg-min/m^3 inhaled GB), differed only slightly from the 12–<25 mg-min/m^3 Injury Profile. Both begin at severity level 3 and remain there until 1000 minutes, at which point they drop to severity level 2. The Injury Profile for clinical presentation 5, however, briefly reached severity level 4 (very severe effects), although this never caused any deaths and therefore did not affect the casualty estimate. The second difference is that the clinical presentation 4 Injury Profile dropped to severity level 1 at 8640 minutes (Day 7), whereas the clinical presentation 5 Injury Profile remained at severity level 2 for the duration of the time specified. There were two reasons for using the clinical presentation 4 Injury Profile to represent severe effects. The first is that the two Injury Profiles were operationally indistinguishable. The second is that the upper limit of the Ct range originally associated with the clinical presentation 5 Injury Profile was tied to the GB LCt_{50} used in *AMedP-8*(*C*) (35 mg-min/m^3). Since a lower value was chosen for *AMedP-7.5* (33 mg-min/m^3), the upper limit of the original *AMedP-8*(*C*) Ct range decreased and the total range over which the Injury Profile applied narrowed. Therefore, the majority of the Ct values that would lead to severe effects fell into the larger range from 12 to <25 mg-min/m^3 inhaled GB.

Last, the *AMedP-7.5* nerve agent inhaled vapor very severe Injury Profile is the same as the *AMedP-8*(*C*) Injury Profile for clinical presentation 6 from Table 29 (originally developed to correspond to ≥30 mg-min/m^3 inhaled GB). All *AMedP-7.5* Injury Profiles for inhaled nerve agents are shown in Table 31.

Table 31. *AMedP-7.5* Nerve Agent Inhaled Vapor Injury Profiles

Time Point (min)	Injury Profile			
	Mild	Moderate	Severe	Very Severe
1	0	2	3	4
3	1	2	3	4
15	1	2	3	4[a]
150	0	2	3	
1000	0	2	2	
1940	0	1	2	
8640	0	1	1	

[a] According to the default value for $T_{death\text{-}CN\text{-}SL4}$, death would be modeled at this point.

Similarly, the *AMedP-7.5* nerve agent percutaneous liquid Injury Profiles, shown in Table 32, are derived from the *AMedP-8*(*C*) VX percutaneous liquid Injury Profiles. The conversion of the *AMedP-8*(*C*) Injury Profiles designated by dose range to the *AMedP-7.5* Injury Profiles based on Injury Severity Level was straightforward. The *AMedP-7.5* nerve agent percutaneous liquid moderate Injury Profile is the same as the *AMedP-8*(*C*) Injury Profile for clinical presentation 1 from Table 30 (originally developed to correspond to 0.8–<1.6 mg VX percutaneous liquid), which was the only Injury Profile that peaked at severity level 2. Likewise, the *AMedP-7.5* nerve agent percutaneous liquid severe Injury Profile is the same as the *AMedP-8*(*C*) Injury Profile for clinical presentation 2 from Table 30 (originally developed to correspond to 1.6–<3.9 mg VX percutaneous liquid), which was the only Injury Profile that peaked at severity level 3. Last, the *AMedP-7.5* nerve agent percutaneous liquid very severe Injury Profile is the same as the *AMedP-8*(*C*) Injury Profile for clinical presentation 3 from Table 30 (originally developed to correspond to ≥3.9 mg VX percutaneous liquid), which was the only Injury Profile that peaked at severity level 4. Because none of the clinical presentations peaked at severity level 1, there is no nerve agent percutaneous liquid mild Injury Profile.

Table 32. *AMedP-7.5* Nerve Agent Percutaneous Liquid Injury Profiles

Time Point (min)	Injury Profile			Time Point (min)	Injury Profile		
	Moderate	Severe	Very Severe		Moderate	Severe	Very Severe
1	0	0	0	100	1	2	
8	0	1	1	150	1	3	
10	1	1	1	360	2	3	
30	1	1	2	1000	1	3	
36	1	1	4	1440	0	3	
51	1	1	4[a]	2400			

[a] According to the default value for $T_{death\text{-}CN\text{-}SL4}$, death would be modeled at this point.

Toxicity Parameters (*AMedP-7.5 Tables 4-1, 4-4, 4-7, 4-10, 4-13, and 4-15*)

12. Best Available Nerve Agent Toxicity Values

Table 33 and Table 34 list for the five nerve agents the toxicity parameter values that were judged to be the best among the available options. The following sections compare the values found in DOD and NATO doctrine and other supporting publications and justify the values in Table 33 and Table 34. There is good overall agreement among doctrine, and the disagreement that exists relates entirely to the generation of new parameter value estimates after the older documents were published. As is reflected in Table 33 and Table 34, all nerve agent toxicity parameter values should be based on the results of Reutter-Wade, Grotte-Yang, or subsequent ECBC research that was designed to fill the knowledge gaps identified by Reutter-Wade (the LLTP and ECBC technical reports).

The values in Table 34 are not all included in *AMedP-7.5*, because the percutaneous liquid route of exposure is considered negligible for all nerve agents modeled except for VX. However, the justifications for excluding percutaneous liquid challenges are based on the values presented in Table 34. In the tables in the next section, the values chosen for *AMedP-7.5* are compared with those in other doctrinal publications. If *AMedP-7.5* does not model the effects of a certain route of exposure, then tables presenting toxicity estimates from different sources are not shown below.

Table 33. Inhaled/Ocular Vapor Toxicity Values for Nerve Agents Used in *AMedP-7.5*

Parameter	GA[a]	GB[b]	GD[b]	GF[b]	VX[b]
LCt_{50}	70	33	33	41[c]	12
PS_{lethal}	12	12	12	12	12
$ECt_{50,severe}$	50	25	25	31	9
PS_{severe}	12[d]	12	12	12	12
$ECt_{50,mild}$	0.4	0.4	0.2	0.4	0.04
PS_{mild}	4.5[e]	4.5	4.5	4.5	4.5
$TLE_{lethal/severe}$	1.5	1.5	1.5	1.25	1
TLE_{mild}	1.5	1.4	1.4	1.4	1.4

[a] Toxicity values from FM 3-11.9.

[b] Toxicity values from the LLTP final report.

[c] "40.9 should be used for extrapolating to longer or shorter exposures."[99]

[d] Changed from 10 probits/log (dose) reported in FM 3-11.9 to 12 probits/log (dose) to be consistent with the values for other nerve agents published in the LLTP final report.

[e] Changed from 10 probits/log (dose) reported in FM 3-11.9 to 4.5 probits/log (dose) to be consistent with the values for other nerve agents published in the LLTP final report.

99 Thomson et al., *Low Level Agent Toxicology*, 530.

Table 34. Percutaneous Liquid Toxicity Values for Nerve Agents Used in or Informing *AMedP-7.5*

Parameter	GA[a]	GB[a]	GD[a]	GF[a]	VX
LD_{50}	1,500	1,700	350	350	3[b]
PS_{lethal}	5	5	6	5	5.5[b]
$ED_{50,severe}$	900	1,000	200	200	2[a]
PS_{severe}	5	5	6	5	6[a]

[a] From FM 3-11.9.

[b] From ECBC-TR-1013.

13. DOD and NATO Doctrine

Table 35 through Table 40 summarize the parameter value estimates in DOD and NATO doctrine for the nerve agents GA, GB, GD, GF, and VX. FM 3-11.9 contains many parameter values for each of the five nerve agents. *AMedP-6*(*C*) does not contain any parameter value estimates for nerve agents. The authors of *AMedP-7.1* have agreed to adopt values used by IDA in the development of *AMedP-7.5*. *AMedP-8*(*C*) and *AMedP-7.5* use parameter value estimates from FM 3-11.9, the LLTP, and ECBC technical reports.

Since the parameter values in the LLTP final report are the most current and the physiological mechanism of toxicity is the same for the lethal and severe level of effects, we assumed that the lethal and severe probit slope values for GA were the same as those published for GB, GD, GF, and VX. Therefore, the GA probit slope for $ECt_{50\text{-}severe}$ of 10 probits/log (dose) published in FM 3-11.9 was changed to 12 probits/log (dose) for use in *AMedP-7.5*.

An individual suffering from mild effects after nerve agent exposure will primarily experience ocular effects and some mild respiratory symptoms. The physiological mechanism of toxicity for mild effects is not exactly the same as that for the other severity levels, and the probit slopes therefore differs. As with the severe probit slope value, we assumed the GA probit slope for $ECt_{50\text{-}mild}$ was the same as the value published in the LLTP final report for the other four nerve agents. Hence, the $ECt_{50\text{-}mild}$ for GA was changed from 10 probits/log (dose) to 4.5 probits/log (dose) for use in *AMedP-7.5*.

Table 35. Inhaled/Ocular Vapor Toxicity Estimates for GA in Doctrine

Parameter	FM 3-11.9	*AMedP-6(C)*	*AMedP-7.1*	*AMedP-8(C)*	*AMedP-7.5*[a]
LCt_{50}	70		70		70
PS_{lethal}	12				12
$ECt_{50,severe}$	50				50
PS_{severe}	10				12[b]
$ECt_{50,mild}$	0.4				0.4
PS_{mild}	10				4.5[c]
$TLE_{lethal/severe}$	1.5				1.5
TLE_{mild}	1.5				1.5

[a] Values from FM 3-11.9.

[b] Changed from 10 probits/log (dose) reported in FM 3-11.9 to 12 probits/log (dose) to be consistent with the values for other nerve agents published in the LLTP final report.

[c] Changed from 10 probits/log (dose) reported in FM 3-11.9 to 4.5 probits/log (dose) to be consistent with the values for other nerve agents published in the LLTP final report.

Table 36. Inhaled/Ocular Vapor Toxicity Estimates for GB in Doctrine

Parameter	FM 3-11.9	*AMedP-6(C)*	*AMedP-7.1*	*AMedP-8(C)*[a]	*AMedP-7.5*[b]
LCt_{50}	35		33	35	33
PS_{lethal}	12			12	12
$ECt_{50,severe}$	25			25	25
PS_{severe}	12			12	12
$ECt_{50,mild}$	0.4			0.4	0.4
PS_{mild}	10			10	4.5
$TLE_{lethal/severe}$	1.5				1.5
TLE_{mild}	1.5				1.5

[a] Values from FM 3-11.9.

[b] Values from the LLTP final report (see Table 41).

Table 37. Inhaled/Ocular Vapor Toxicity Estimates for GD in Doctrine

Parameter	FM 3-11.9	*AMedP-6(C)*	*AMedP-7.1*	*AMedP-8(C)*	*AMedP-7.5*[a]
LCt_{50}	35		33		33
PS_{lethal}	12				12
$ECt_{50,severe}$	25				25
PS_{severe}	12				12
$ECt_{50,mild}$	0.2				0.2
PS_{mild}	10				4.5
$TLE_{lethal/severe}$	1.25				1.5
TLE_{mild}	1.4				1.4

[a] Values from the LLTP final report (see Table 41).

Table 38. Inhaled/Ocular Vapor Toxicity Estimates for GF in Doctrine

Parameter	FM 3-11.9	*AMedP-6(C)*	*AMedP-7.1*	*AMedP-8(C)*	*AMedP-7.5*[a]
LCt_{50}	35				41[b]
PS_{lethal}	12				12
$ECt_{50,severe}$	25				31
PS_{severe}	10				12
$ECt_{50,mild}$	0.2				0.4
PS_{mild}	10				4.5
$TLE_{lethal/severe}$	1.25				1.25
TLE_{mild}	1.4				1.4

[a] Values from the LLTP final report (see Table 41).

[b] "40.9 should be used for extrapolating to longer or shorter exposures."[100]

Table 39. Inhaled/Ocular Vapor Toxicity Estimates for VX in Doctrine

Parameter	FM 3-11.9	*AMedP-6(C)*	*AMedP-7.1*	*AMedP-8(C)*[a]	*AMedP-7.5*[b]
LCt_{50}	15		12	15	12
PS_{lethal}	6			6	12
$ECt_{50,severe}$	10			10	9
PS_{severe}	6			6	12
$ECt_{50,mild}$	0.1			0.1	0.04
PS_{mild}	4			4	4.5
$TLE_{lethal/severe}$	1				1
TLE_{mild}					1.4

[a] Values from FM 3-11.9.

[b] Values from the LLTP final report (see Table 41).

Table 40. Percutaneous Liquid Toxicity Estimates for VX in Doctrine

Parameter	FM 3-11.9	*AMedP-6(C)*	*AMedP-7.1*	*AMedP-8(C)*[a]	*AMedP-7.5*
LD_{50}	5		3	5	3[b]
PS_{lethal}	6			6	5.5[b]
$ED_{50,severe}$	2			2	2[a]
PS_{severe}	6			6	6[a]

[a] Values from FM 3-11.9.

[b] Values from ECBC-TR-1013 (see Table 42).

100 Thomson et al., *Low Level Agent Toxicology*, 530.

14. Supporting Publications and Implementations

The only recent research intended to provide new parameter value estimates for inhaled nerve agents was the LLTP. Table 41 summarizes the recommendations from the LLTP, which include an emphasis on the importance of using the toxic load exponents when extrapolating to exposures longer or shorter than 2 minutes.

Table 41. Inhaled/Ocular Vapor Toxicity Estimates from the LLTP

Parameter	GB	GD	GF	VX
LCt_{50}	33	33	41[a]	12
PS_{lethal}	12	12	12	12
$ECt_{50,severe}$	25	25	31	9
PS_{severe}	12	12	12	12
$ECt_{50,mild}$	0.4	0.2	0.4	0.04
PS_{mild}	4.5	4.5	4.5	4.5
$TLE_{lethal/severe}$	1.5	1.5	1.25	1
TLE_{mild}	1.4	1.4	1.4	1.4

[a] "40.9 should be used for extrapolating to longer or shorter exposures."[101]

Table 42 summarizes the recommendations from recent research focused on updating percutaneous liquid toxicity estimates for VX. ECBC-TR-1013 states in its abstract that it supersedes all previous estimates; both of its estimates are different from those in FM 3-11.9.

HPAC implements the recommendations from the LLTP, where available. Where there is no LLTP recommendation, HPAC implements the values from FM 3-11.9.

Table 42. Percutaneous Liquid Toxicity Estimates for VX in ECBC Technical Reports

Parameter	ECBC-TR-795	ECBC-TR-1013
LD_{50}	3	3
PS_{lethal}	6	5.5
$ED_{50,severe}$	2	
PS_{severe}	6	

Estimation of "Moderate" Nerve Agent Toxicity Values

Correctly allocating individuals among the Injury Profiles requires a unique probit model for each symptom severity level, which describes the likelihood of manifesting symptoms of at least that severity as a function of the challenge. Table 33 enumerates for all five nerve agents the ECt_{50} and probit slope values that specify a probit model for mild,

101 Ibid.

severe, and lethal (very severe) inhalation/ocular effects, but parameter values associated with moderate symptoms are not published by other sources. To associate individuals exhibiting moderate effects to an appropriate Injury Profile, we used the existing probit model parameter values for other symptom severity levels to estimate moderate inhalation ECt_{50} and probit slope values for the five nerve agents.

Since the primary mechanism of nerve agent toxicity does not vary among moderate, severe, and lethal effects, we assumed that the moderate probit slope is equal to the lethal and severe probit slopes for the five nerve agents. The assumption also helps avoid illogical results such as two toxicity curves intersecting. For all five nerve agents, *AMedP-7.5* uses 12 probits/log (dose) as the probit slope for severe and lethal effects, so this value was also chosen as the probit slope for moderate effects. Given a probit slope, knowing any single point on the probit curve will specify the model, and the $ECt_{50\text{-moderate}}$ value can be calculated. For the nerve agents in *AMedP-8*(*C*) (GB and VX), the lower bound of the nerve agent inhaled vapor Injury Profile for clinical presentation 2 (see Table 29) was assumed to be equal to the $ECt_{16\text{-moderate}}$. This Injury Profile is the least severe Injury Profile from *AMedP-8*(*C*) that resulted in moderate symptoms and originally corresponded to 1–6.5 mg-min/m^3 inhaled GB or 0.3–2 mg-min/m^3 inhaled VX. Therefore, the GB $ECt_{16\text{-moderate}}$ was assumed equal to 1 mg-min/m^3, and the VX $ECt_{16\text{-moderate}}$ was assumed equal to 0.3 mg-min/m^3.

Given the $ECt_{16\text{-moderate}}$ and the probit slope, *AMedP-7*.5 Equation 4-1 was used to solve for the $ECt_{50\text{-moderate}}$. As shown in the calculations below, the $ECt_{50\text{-moderate}}$ values were calculated as 1.2 mg-min/m^3 for GB and 0.36 mg-min/m^3 for VX.

$$p_{Q\_k,n} = \Phi\left(PS_{Q\_k} \cdot \log_{10}\left(\frac{X_{Q,n}^{eff}}{ECt_{50,Q\_k}}\right)\right)$$

$$0.16 = \Phi\left(12 \cdot \log_{10}\left(\frac{1}{ECt_{50,GB\_moderate}}\right)\right)$$

$$ECt_{50,GB\_moderate} = 1.2$$

$$0.16 = \Phi\left(12 \cdot \log_{10}\left(\frac{0.3}{ECt_{50,VX\_moderate}}\right)\right)$$

$$ECt_{50,VX\_moderate} = 0.36$$

Since GA, GD, and GF were not modeled in *AMedP-8*(*C*), there were no challenge ranges pre-established for these agents. Because GA, GB, and GF all had the same value for the $ECt_{50\text{-mild}}$ (0.4 mg-min/m^3), the $ECt_{16\text{-moderate}}$ value of 1 mg-min/m^3 for GB was also assumed for GA and GF, resulting in the same $ECt_{50\text{-moderate}}$ value of 1.2 mg-min/m^3 for these agents. Since the GD $ECt_{50\text{-mild}}$ value was half that of GB, the $ECt_{16\text{-moderate}}$ value was set equal to 0.5 mg-min/m^3, resulting in an $ECt_{50\text{-moderate}}$ value of 0.6 mg-min/m^3 for GD.

Table 43 summarizes the moderate inhaled/ocular vapor toxicity values derived for use in *AMedP-7.5*. Here we emphasize that we do not recommend these values be used outside of *AMedP-7.5*; we would have preferred to use values provided by toxicology experts and supported by specific data rather than the process we used, if it had been possible to do so.

Table 43. Inhaled/Ocular Vapor Toxicity Values for Nerve Agents Used in *AMedP-7.5*

Parameter	GA	GB	GD	GF	VX
$ECt_{50,moderate}$	1.2	1.2	0.6	1.2	0.36
$PS_{moderate}$	12	12	12	12	12

The same process was used to estimate the necessary probit model parameters for liquid nerve agent challenges. Liquid challenge was neglected for all nerve agents except VX, for which there are three Injury Profiles: moderate, severe, and lethal. Table 34 specifies the published probit model parameter values for severe and lethal percutaneous liquid VX effects. Thus, we only needed to estimate moderate probit model parameters to calculate the probability of an individual following the moderate VX liquid Injury Profile. The moderate percutaneous liquid VX probit slope was assumed to be 6 probits/log (dose), the same value as the severe probit slope. The *AMedP-8*(*C*) VX percutaneous liquid Injury Profile that peaks at severity level 2 (moderate) symptoms (see Table 30) was originally developed to correspond to 0.8–<1.6 mg. Following the same logic as for the inhalation/ocular probit model parameter estimation, the VX $ED_{16\text{-moderate}}$ was assumed equal to 0.8 mg. The resulting $ED_{50\text{-moderate}}$ value, as shown below, was calculated to be 1.2 mg.

$$0.16 = \Phi\left(6 \cdot \log_{10}\left(\frac{0.8}{ED_{50,VX\_moderate}}\right)\right)$$

$$ED_{50,VX\_moderate} = 1.2$$

Medical Treatment (*AMedP-7.5 Tables 4-3, 4-6, 4-9, 4-12, and 4-17*)

To treat the harmful effects of nerve agents, NATO member countries issue nerve agent antidote kits to military service members operating in an area where these agents pose a potential hazard.[102] Three types of drugs are typically used to treat nerve agent poisoning: an anticholinergic (typically atropine), an oxime reactivator, and an anti-convulsant. Given the instant availability of nerve agent treatments on the battlefield, the *AMedP-7.5* treatment model assumes that self-aid/buddy-aid is performed at the time of

102 North Atlantic Treaty Organization (NATO), *AMedP-6*(*C*) *Volume III: NATO Handbook on the Medical Aspects of NBC Defensive Operations* (*Chemical*), STANAG 2463 (Brussels: NATO, 14 December 2006), 2–21.

symptom onset. Further treatment, if modeled, is assumed to begin within 30 minutes of symptom onset.

Table 44. *AMedP-7.5* Nerve Agent Treatment Model

Injury Profile	DOW[a]	CONV[a]	RTD[a]
Mild	0%	Day 2: 100%	Day 8: 100%
Moderate	0%	Day 3: 100%	Day 15: 100%
Severe	0%	Day 4: 50% Day 5: 50%	Day 31: 100%
Self-aid/buddy aid only:			
Very Severe, dose < 3×LD_{50}	0%	Day 15: 100%	0%
Very Severe, dose ≥ 3×LD_{50}	Day 2: 100%	0%	0%
Self-aid/buddy aid + further medical treatment:			
Very Severe, dose < 5×LD_{50}	0%	Day 15: 100%	0%
Very Severe, dose ≥ 5×LD_{50}	Day 2: 100%	0%	0%

Note: The Very Severe models in this table will only apply for GD if PB pretreatment is also used; otherwise, any casualty in the Very Severe category will be modeled as KIA.

[a] Reported values indicate the fraction that changes status on a given day; they are not cumulative.

The nerve agent treatment model parameter values in Table 44 (*AMedP-7.5* Tables 4-3, 4-6, 4-9, 4-12, and 4-17) reflect data from reports of both accidental and experimental human nerve agent exposures and the inputs of SMEs. Table 45 provides a summary of articles reporting pertinent human nerve agent exposures that we used in developing the model. The symptom descriptions for many of these cases were compared to the nerve agent casualty descriptions in *MACW* and the *AMedP-7.5* Injury Profiles to approximate the severity of exposure and inform the duration of treatment and the expected time until patients convalesce or RTD.

In addition to reviewing the literature, we met with staff at USAMRICD to review the medical treatment parameter values. USAMRICD personnel present at the meeting were Dr. Charles Hurst, Mr. Timothy Byrne, and Dr. John McDonough. The USAMRICD researchers recommended that the hospital discharge times from the literature be modeled not as the time of RTD, but rather as the time at which individuals begin convalescence, reasoning that a soldier would not RTD without a convalescent period, even following a mild nerve agent exposure.

Table 45. Reported Human Exposures to Nerve Agents or Organophosphorus (OP) Pesticides

Exposure type	Agent	Exposure route(s)	Source
Accident	GB	Inhalational	Clanton and Ward, 1952
Accident	GB	Inhalational	Gaon and Werne, 1955
Accident	GB	Inhalational, percutaneous, oral	Grob, 1956
Experiment	GB	Oral, intra-arterial, conjunctival	Grob and Harvey, 1958
Accident	Parathion	Inhalational, oral	Durham and Hayes, 1962
Accident	GB, GD	Inhalational, oral/dermal	Sidell, 1974
Accident	VX, GB	Oral, IV	Sidell and Groff, 1974
Terrorism	VX	Percutaneous	Nozaki et al., 1995a
Terrorism	GB	Inhalational	Nozaki et al., 1995b
Terrorism	GB	Inhalational	Okumura et al., 1996
Terrorism	GB	Inhalational	Nakajima et al., 1997
Terrorism	GB	Inhalational	Ohbu et al., 1997
Terrorism	GB	Inhalational	Okudera et al., 1997
Accident	OP pesticides	Oral	Balali-Mood and Shariat, 1998
War	GA, GB	Inhalational	Helm, 1999
Terrorism	GB	Inhalational	Okudera, 2002
War	GA, GB	Inhalational	Newmark, 2004

*Note: S*ome cases are reported in more than one of the above sources.

The *AMedP-7.5* Mild inhaled nerve agent Injury Profile cohort has symptoms consistent with the *MACW* descriptions of minimal and mild exposures.[103] For minimal exposures, "if liquid exposure can be excluded, there is no reason for prolonged observation,"[104] and even without treatment, the symptoms of minimal or mild exposures would dissipate within a day.[105] This is confirmed by Sidell,[106] who described three mild cases of accidental sarin inhalation that all healed without therapy. After six hours of observation, the three patients were discharged with only slight eye irritation and decreased vision in dim light. Nozaki et al.[107] reported mild symptoms among 13 emergency room

103 Sidell, Newmark, and McDonough, "Nerve Agents," 191–192.

104 Ibid., 192.

105 Curling et al., *Technical Reference Manual*, 76–77, 82–83.

106 Frederick R. Sidell, "Soman and Sarin: Clinical Manifestations and Treatment of Accidental Poisoning by Organophosphates," *Clinical Toxicology* 7, no. 1 (1974).

107 H. Nozaki et al., "Secondary Exposure of Medical Staff to Sarin Vapor in the Emergency Room," *Intensive Care Medicine* 21, no. 12 (1995).

doctors treating victims of the Tokyo subway sarin attacks. Fewer than half were treated with atropine (and one additionally received 2-PAM iodide), but all were able to continue working through their symptoms. The last symptom to resolve, dim vision, lasted from 2 to 12 hours in most patients, but did persist for 2 days in two patients. A summary of the treatment of 640 victims from the same attack was reported by Okumura et al.[108] Most (528) of these patients exhibited only mild symptoms and were released after a maximum of 12 hours of observation. Because most symptoms will likely resolve by the end of the first day with or without treatment, individuals following the mild Injury Profile are modeled to enter a period of convalescence on Day 2. USAMRICD personnel recommended that soldiers RTD on Day 8, a week after the exposure.

Okumura et al. described a second group of 107 patients with symptoms in addition to the mild ocular symptoms previously discussed, but not severe enough to require intubation or result in loss of consciousness.[109] After treatment with atropine and 2-PAM (and in some cases diazepam), all but two of those patients were discharged within 2 to 4 days[110] (the mean duration in the hospital for that group was 2.4 days[111]), although at the time of discharge, more than 60% of patients still complained of eye symptoms and more than 20% complained of headache.[112] The symptom progressions of the patients in that group are assumed to align with the *AMedP-7.5* moderate and severe Injury Profiles, but there is no way to clearly differentiate between them.

The *AMedP-7.5* moderate inhaled and percutaneous nerve agent Injury Profiles have symptoms that generally match those of moderate exposures described by *MACW*.[113] That reference recommends that "casualties with this degree of exposure should be observed closely for at least 18 hours after the onset of signs and symptoms." According to a 1958 article by Grob and Harvey describing experimental administration of sarin to volunteers, "moderately severe symptoms lasted 5 to 24 hours"[114] following oral sarin administration, but it is unclear whether all symptoms were absent after those time frames. In a later

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108 Tetsu Okumura et al., "Report on 640 Victims of the Tokyo Subway Sarin Attack," *Annals of Emergency Medicine* 28, no. 2 (1996).

109 Okumura et al., "Report on 640 Victims," 131.

110 Ibid., 134.

111 Ibid., 131.

112 Ibid., 131.

113 Sidell, Newmark, and McDonough, "Nerve Agents," 192.

114 David Grob and John C. Harvey, "Effects in Man of the Anticholinesterase Compound Sarin (Isopropyl Methyl Phosphonofluoridate)," *The Journal of Clinical Investigation* 37, no. 3 (March 1958), 355.

experiment, volunteers exposed to intravenous VX that experienced nausea/vomiting had apparently recovered within the 48-hour timeframe of the experiment.[115]

This evidence from the literature suggests that individuals with moderate symptoms of nerve agent poisoning would not be discharged from the hospital on the same day they were exposed and would at least remain under observation into the second day. This reflects the recommended 18+ hours observation period,[116] the 5–24 hour symptomatic period,[117] and the low end of the range of discharge times (2–4 days) reported by Okumura et al.[118] Thus, patients in an *AMedP-7.5* Moderate nerve agent Injury Profile are reported to convalesce on Day 3, reflecting a hospitalization period that extends into the day after exposure and casualty reporting according to Table 15. For these individuals, USAMRICD personnel recommended that the convalescent period be modeled to last until the end of the second week, so moderate nerve agent patients are estimated to RTD on Day 15.

The *AMedP-7.5* Severe nerve agent Injury Profiles reflect the most severe outcomes that are nonlethal without treatment. They are characterized by severe respiratory, muscular, and/or ocular effects and brief lapses of consciousness. Under the assumption that of the patients in the group of 107 victims of the Tokyo sarin attack described by Okumura et al.,[119] those experiencing severe symptoms were on the higher end of the reported range of discharge times (2–4 days), individuals in an *AMedP-7.5* Severe nerve agent Injury Profile cohort are modeled to convalesce on Day 4 and 5 (equal probability of convalescing on either day). This reflects a release from hospitalization at some point on days 3 or 4 (per Table 15).

MACW notes:

> a soldier who has had signs of severe exposure with loss of consciousness, apnea, and convulsions, may have milder CNS [central nervous system] effects for many weeks after recovery from the acute phase of intoxication. Except in dire circumstances, return to duty during this time period should not be considered for such casualties.[120]

Consistent with this advice, USAMRICD personnel recommended modeling a month-long convalescent period for these patients, so individuals following the *AMedP-7.5* severe nerve agent Injury Profiles are modeled to RTD on Day 31.

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115 Frederick R. Sidell and William A. Groff, "The Reactivatibility of Cholinesterase Inhibited by Vx and Sarin in Man," *Toxicology and Applied Pharmacology* 27 (1974).

116 Sidell, Newmark, and McDonough, "Nerve Agents," 192.

117 Grob and Harvey, "Effects in Man," 355.

118 Okumura et al., "Report on 640 Victims," 134.

119 Okumura et al., "Report on 640 Victims," 134.

120 Sidell, Newmark, and McDonough, "Nerve Agents," 194.

Individuals assigned to the very severe Injury Profiles are modeled as fatalities without treatment since they remain at severity level 4, very severe, for more than 15 minutes. Yet, it is reasonable to assume that with treatment, many of these casualties would recover. In fact, of 10 individuals reported in the literature that lost consciousness and required artificial respiration after nerve agent exposure, 8 were effectively treated.[121] One of the two fatalities was neither conscious nor breathing and was pronounced dead at the emergency room after no response to 30 minutes of CPR; the second died of "severe hypoxic brain damage" 28 days post-exposure.[122]

To model the increased survivability with treatment, a protection ratio, like those derived from animal studies, was applied to humans, creating a threshold above which individuals would be modeled to die even with treatment. A review of the literature revealed that no data from which to determine an appropriate protection ratio were available. More than 30 documents on non-human primate exposures were ruled out due to the following limitations:

- Antidotes were given *before* the onset of symptoms (over 50% of reports).
- Dose of anticholinergic, oxime, and/or anticonvulsant was much higher than the doses fielded in autoinjectors by NATO forces.
- Specific set of antidotes used was not an anticholinergic, an oxime, or an anticonvulsant; either a subset of the three, or some additional drug, was used.
- Agent challenge was only 1 or $2\times LD_{50}$.

With an understanding of the limitations of the published literature, the USAMRICD personnel estimated that for self-aid/buddy aid alone, a reasonable threshold dose for survival, to be applied to GA, GB, GD, GF, and VX, was $3\times LD_{50}$. The analogous estimate for self-aid/buddy aid plus further medical treatment was $5\times LD_{50}$. For GD, these thresholds would only apply if PB pretreatment was also used; without PB, $1\times LD_{50}$ will be used. Although USAMRICD personnel acknowledged that in reality, the specific biochemistry of each nerve agent will result in different thresholds per agent, the estimates of $3\times LD_{50}$ and $5\times LD_{50}$ were deemed suitable as generic estimates for the purpose of the *AMedP-7.5* model.

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121 B.R. Clanton and J.R. Ward, "Case Report of a Severe Human Poisoning by GB," (Dugway Proving Ground, MD: Chemical Corps Medical Laboratories, 1952); David Grob, "The Manifestations and Treatment of Poisoning Due to Nerve Gas and Other Organic Phosphate Anticholinesterase Compounds," *Archives of Internal Medicine* 98, no. 2 (1956); Nozaki et al., "Secondary Exposure of Medical Staff"; Okumura et al., "Report on 640 Victims"; Sidell, "Soman and Sarin"; Sidell, Newmark, and McDonough, "Nerve Agents."

122 Okumura et al., "Report on 640 Victims," 132–133.

As reflected in Table 44, at the direction of USAMRICD personnel, for any dose above the threshold, casualties are modeled to die within a day.[123] USAMRICD personnel also recommended that survivors be modeled to require 2 weeks of treatment in an MTF before being stable enough to be transferred to a Role 4 treatment facility; they are modeled to never RTD. This is roughly consistent with the median discharge time for the survivors among 10 very severe cases reported in the literature. On the lower end, three individuals were reportedly discharged on days 3, 5, and 6.[124] In another case, it was unclear when the patient was discharged, but symptoms were present through Day 4 and blood tests results were reported daily through Day 12 (and less frequently thereafter for 55 days).[125] Nozaki et al. reported a very severe case that was discharged on Day 15.[126] Another very severe case of GB inhalation resulted in a discharge on Day 20 to another hospital.[127] Finally, of the two very severe cases reported by Sidell, one was discharged 4 weeks post-exposure, and the discharge date of the second case was unspecified.[128]

123 USAMRICD personnel reasoned that either treatment would resolve respiratory failure, and the individual would survive, or it would not, and the patient would die within the day.

124 Okumura et al., "Report on 640 Victims."

125 Grob, "Manifestations and Treatment of Poisoning."

126 Nozaki et al., "Case of VX Poisoning."

127 Clanton and Ward, "Severe Human Poisoning by GB."

128 Sidell, "Soman and Sarin"; Sidell, Newmark, and McDonough, "Nerve Agents."

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1.7. HD Model (*AMedP-7.5 Section 4.2.7*)

Introduction

The objective of this chapter is to describe the human response methodology for HD as it has been incorporated into the *AMedP-7.5* methodology.

The first section lists the modeling assumptions inherent in the *AMedP-7.5* methodology for HD. Next, the chapter describes the physiological effects of HD. The next section discusses the four steps taken to develop the nerve agent Injury Profiles for *AMedP-7.5*: (1) match the symptoms within each physiological system to the defined Injury Severity Levels; (2) develop the symptom progressions used in *AMedP-8*(*C*), which are tables of the Injury Severity Level over time corresponding to each physiological system; (3) combine the symptom progressions to generate the *AMedP-8*(*C*) Injury Profiles; and (4) map the *AMedP-8*(*C*) Injury Profiles to the *AMedP-7.5* Injury Profiles. The following section lists the toxicity values found in the literature for HD, which are used in *AMedP-7.5* to determine the probabilistically derived proportions of individuals in each Injury Profile category. Last, the medical treatment model for HD is discussed.

Assumption (*AMedP-7.5 Section 4.2.7.2*)

> **Assumption**: Human response due to inhaled HD, percutaneous HD vapour, and percutaneous HD liquid are independent of one another—the effects of each challenge type are modeled separately and only combined in the form of Composite Injury Profiles and the Equivalent Percutaneous Vapour challenge type.

This is the same as assuming that exposure to inhaled HD vapor, percutaneous HD vapor, and percutaneous HD liquid are not synergistic. Although data exist that indicate that simultaneous injuries caused by multiple simultaneous insults may result in higher injury severity than would result from any single insult alone,[129] not enough information currently exists to determine the extent to which HD injury severity might be expected to change.

Physiological Effects (*AMedP-7.5 Tables 4-19, 4-21, and 4-23*)[130]

HD is a vesicant that primarily produces local effects in regions of the body that are exposed to the external environment: the skin, eyes, and the respiratory system are typically

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129 Levin, *Effect of Combined Injuries*; and U.S. Department of the Army, *Personnel Risk and Casualty Criteria for Nuclear Weapons Effects*, Army Pamphlet 50-7 (Washington, DC: U.S. Department of the Army, 1 October 2013), Appendix F.

130 This section is largely paraphrased from the following two sources: Hurst et al., *Medical Management of Chemical Casualties*, 64–80; and Charles G. Hurst et al., "Vescants," chap. 8 in *Medical Aspects of Chemical Warfare*, ed. Shirley D. Tuorinsky, Textbooks of Military Medicine

the most severely affected, though (less commonly) systemic effects may also occur. HD may produce systemic effects on the upper and lower gastrointestinal tract, the hematopoietic system, as well as the central nervous system.

The effects of skin contact with HD vapors or liquid can result in erythema accompanied by an itching or burning sensation. These initial signs and symptoms typically manifest 4 to 8 hours post-exposure, but can appear as early as 1 hour and later than 48 hours post-exposure depending on the dose received. If the disease does not progress beyond this stage, then recovery can be expected within several days. At higher vapor doses and in cases where there is skin contact with liquid HD, the disease may progress to the formation of vesicles (fluid-filled blisters) on the skin beginning 2 to 18 hours after the initial manifestation of symptoms and continuing for several days. Contact with liquid HD can produce necrotic lesions that are surrounded by vesicles. Once the injury has progressed to this stage, recovery can be expected to require weeks to months. The magnitude of skin disease is highly dependent on the exposed location on the body, the presence of moisture on the skin, and the ambient temperature. Areas of the body in which the skin is thin, moist, or warm are more susceptible to disease. As a result, the genitals, armpits, and neck are often the most severely affected.

The eyes are particularly sensitive to HD, and ocular effects produced by HD exposure are the most likely to incapacitate. The ocular signs and symptoms of HD exposure are usually present before the onset of skin effects. The initial ocular effects generally involve eye irritation with a concurrent reddening of the eye and photophobia. At high vapor doses and instances of liquid exposure, the eyes may develop severe conjunctivitis, blepharospasm (uncontrolled twitching of the eyelids), and corneal damage involving edema and scarring.

The regions of the pulmonary system affected by the inhalation of HD vapors depend on the dose. Low-dose exposures may only cause irritation and erythema to the nose, sinuses, and pharynx. Other mild effects include runny nose, sneezing, nose bleed, and a dry unproductive cough. At higher doses, areas that are lower in the respiratory tract become affected and result in laryngitis, sputum-producing cough, as well as a feeling of tightness in the chest. At even higher doses, the most severe symptoms involve dyspnea and sloughing of the airway's epithelial tissue. This sloughed tissue and mucus can block airways, resulting in atelectasis (collapse of the lung). Pulmonary edema does not often develop, but is sometimes seen in terminal cases accompanied by hemorrhaging.

Upper gastrointestinal signs and symptoms are generally not severe at their onset, which often occurs around the time that the skin effects become apparent. Nausea and

(Washington, DC: Office of the Surgeon General, Borden Institute, Walter Reed Army Medical Center, 2008), 266–276.

vomiting are the most common symptoms, and these usually last less than 24 hours, but may reappear several days later. Lower gastrointestinal effects such as diarrhea have been reported in laboratory animal experiments when HD is administered intravenously, but this is not an expected route of exposure in the event of a chemical warfare attack. Lower gastrointestinal effects are not common with human inhalation or percutaneous exposures. In fact, reports of lower gastrointestinal effects are often conflicting, with differing reports of both diarrhea and constipation.

HD seems to affect the central nervous system rather mildly. Low-dose HD exposures may cause lethargy, apathy, and depression. These effects on the central nervous system are mild. Although some laboratory animal experiments indicate that higher doses can cause hyperexcitability, abnormal muscular movements, and convulsions, there is little evidence of these more serious effects in human exposures.

The most significant effect of HD on the hematopoietic system is a decreased number of leukocytes. This reduces the ability to fight off the secondary infections (immunosuppression) that are likely to occur, considering the damage to the skin and respiratory system.

There are three mechanisms for death as a result of HD exposure. Rapid deaths, in the first several minutes post-exposure, result from the extremely high doses of HD. These high doses produce an acetylcholinergic reaction in the body and effectively paralyze the respiratory system; individuals die of asphyxiation. Individuals could alternatively develop pneumonia and potentially die due to a combination of the infection in the lungs and sepsis at approximately 3–6 days post-exposure. The last mechanism for death is also a result of internal sepsis: high percutaneous doses of liquid HD result in bone marrow suppression. Eventually, approximately 1 to 3 weeks post-exposure, the exposed individual's body begins to deteriorate due to its suppressed immune system and inability to fight off infection.

Injury Profiles (*AMedP-7.5 Tables 4-20, 4-22, and 4-24*)

The basic concept of the *AMedP-7.5* methodology is that an individual is considered a casualty at the time of first onset of a specified Injury Severity Level, based on specific symptoms resulting from exposure to the causative agent. The human response component of the methodology specifies an Injury Profile depicting Injury Severity Level over time that is used to determine whether an individual is declared KIA, WIA, or DOW and thereby considered to be a casualty and, if so, at what point this would occur. The Injury Profiles for chemical agents included in *AMedP-8*(*C*) were derived from symptom progressions, which show the severity level of symptoms in the system in which they manifest (as

opposed to the causative system) over time.[131] The severity level of the Injury Profile at any given time point corresponds to the worst severity level experienced in any of the representative physiological systems at that time. The nature of symptoms and their times of onset depend on the agent. The following sections explain the historical development of the HD symptom progressions and Injury Profiles in *AMedP-8*(*C*) and how they were adapted for use in *AMedP-7.5*.

Severity Levels

As mentioned in Chapter 1, the *AMedP-7.5* chemical agent methodology built on the DNA Improved Casualty Estimation (DICE) methodology for estimating human performance. For HD, the DICE methodology employed four physiological systems to represent the injury progression: systemic, respiratory, ocular, and skin. These symptoms were represented on a severity scale of 1–5.[132]

During the development of *AMedP-8*(*C*), in an effort to ensure clarity and consistency, the symptoms and systems for HD were correlated to four representative physiological systems—upper gastrointestinal, respiratory, ocular, and skin—in which symptoms would be expected to manifest following exposure to chemical agents. The applicable systems are shown in Table 46.

Table 46. Blister Agent Route of Exposure Correlation to Representative Physiological Systems

System	HD Inhalation	HD Ocular	HD Equivalent Percutaneous
Ocular		X	
Respiratory	X		
Skin			X
Upper Gastrointestinal	X		

The DICE human response methodology correlated the severity levels for each of the four physiological systems to anticipated signs and symptoms; the severity levels were independent for each physiological system. For example, an ocular severity of 4 (described as “temporary blindness”) while operationally challenging, was not, however, equivalent to a respiratory severity of 4 (“breathing stops completely”) which could potentially kill an individual.

131 Injury profiles for chemical agents incorporated into the methodology after the publication of *AMedP-8*(*C*)—namely, all chemical agents other than nerve agents and HD—were derived for the whole body rather than the underlying physiological systems. Therefore, no symptom progressions were created for those agents.

132 Anno et al., *Performance on Infantry and Artillery Personnel*, 8–13; McClellan, Anno, and Matheson, *Chemical Agent Exposure and Casualty Estimation*, 11–16; and Deverill and Metz, *DICE Chemical Insult Program*, 44–74.

In contrast, symptoms in the *AMedP*-(*C*) methodology were expressed on a single scale of 0–4, with 0 representing no observable injury and 4 representing very severe effects *independent of the physiological system*. To align the severities across the physiological systems and be able to draw useful Injury Profiles, *AMedP-8*(*C*) used adjusted severity levels associated with each set of signs and symptoms. As a result, all four physiological systems begin with a "no observable effect" level, but each system has only the number of severity levels necessary to achieve the maximum severity at which signs and symptoms for that physiological system occur. For example, if a given physiological system was not expected to manifest symptoms greater in severity than level 3, then the scale for that system would range from 0 to 3. Moreover, the new severity levels are aligned so that, for instance, an Injury Severity Level 3 ocular injury consists of signs and symptoms of equal severity to those found in Injury Severity Level 3 for the respiratory system and Injury Severity Level 3 for the upper gastrointestinal system. Again, these signs and symptoms are shown in the physiological system in which they manifest, rather than in the causative system. The *AMedP-8*(*C*) symptom-severity level correlations are shown in Table 47 for HD.

Table 47. HD Symptoms Severity Levels

Severity	Ocular	Respiratory
0	No observable injury	No observable injury
1	Irritation with eye pain; conjunctival erythema and/or edema	Mild shortness of breath; tight chest, coughing, and runny nose
2	Eye pain and/or irritation with conjunctival erythema and/or edema; blepharospasm; difficulty opening the eyes; sensitivity to light	Frank shortness of breath; difficult to breathe, wheezing breath, respiratory congestion, bronchorrhea
3	Severe eye inflammation and pain leading to an inability to open the eyes	Severe dyspnea
4		Breathing stops completely or struggling to breathe; prostration

Table 47. HD Symptoms Severity Levels (continued)

Severity	Skin	Upper Gastrointestinal
0	No observable injury	No observable injury
1	Skin sensitive to touch in crotch, armpits, and on inside of elbow and knee joints	Upset stomach and nausea; watering mouth and frequent swallowing to avoid vomiting
2	Skin sore in crotch, armpits, elbow and knee joints, and painful when moving, red swollen skin, tiny blisters on hands and neck	Episodes of vomiting, possibly including dry heaves; severe nausea and possibility of continued vomiting
3	Skin raw and painful in crotch, armpits, elbow and knee joints, red swollen body skin, large blisters on hands and neck	
4	Skin sloughage after blisters or swollen skin	

Symptom Progressions

Using the new severity level scales, the authors of *AMedP-8*(*C*) adapted existing descriptions from the DICE methodology of symptom severity level changes over time for HD for each of the four physiological systems—ocular, respiratory, skin, and upper gastrointestinal. The resulting symptom progressions represented clinically differentiable human responses to HD exposure. In 2008, SMEs at an international chemical agent human response meeting in Munich, Germany, reviewed these symptom progressions and agreed on the final versions to be included in the *AMedP-8*(*C*) methodology.[133] Table 48 through Table 53 present the agreed-upon symptom progressions for inhaled HD vapor (manifested in the respiratory and upper GI systems). Table 54 presents the symptom progressions resulting from ocular HD challenge, and Table 55 presents the symptom progressions for equivalent percutaneous HD vapor (manifested in the skin). Last, to represent the lethal impact of internal sepsis resulting from high percutaneous liquid HD doses, NATO HD SMEs at the chemical review meeting recommended an additional symptom progression ending in death at 336 hours, which is shown in Table 56.[134] Although sepsis would likely result in multiple organ failure syndrome, the symptom progression was modeled to manifest in the respiratory system.

The "no observable effect" progressions are not shown; all severity levels would be 0 for the duration of time observed. Although these different symptom progressions were originally linked to challenge ranges in *AMedP-8*(*C*), that information is excluded in this TRM because *AMedP-7.5* uses only the clinical presentations. As a result, they are labeled below on an arbitrary scale as "Presentation 1" through "Presentation #," where # is the

133 Burr et al., *Chemical Human Response*, 1–71.

134 Ibid.

total number of symptom progressions for a given route of exposure. A higher number represents a worse clinical presentation.

Table 48. Symptom Progressions by Physiological System Developed for *AMedP-8*(*C*) for HD Inhaled Vapour Clinical Presentation 1

Time Point (hr)	Respiratory	Upper GI
1	0	0
8	0	1
20	0	0

Table 49. Symptom Progressions by Physiological System Developed for *AMedP-8*(*C*) for HD Inhaled Vapour Clinical Presentation 2

Time Point (hr)	Respiratory	Upper GI
1	0	0
6	0	1
18	1	1
48	1	0
168	0	0

Table 50. Symptom Progressions by Physiological System Developed for *AMedP-8*(*C*) for HD Inhaled Vapour Clinical Presentation 3

Time Point (hr)	Respiratory	Upper GI
1	0	0
6	0	1
10	1	1
36	2	1
48	2	0
336	1	0
720	0	0

Table 51. Symptom Progressions by Physiological System Developed for *AMedP-8*(*C*) for HD Inhaled Vapour Clinical Presentation 4

Time Point (hr)	Respiratory	Upper GI
1	0	1
6	0	2
10	1	2
24	2	2
36	3	1
336	2	1
720	1	0
1008	0	0

Table 52. Symptom Progressions by Physiological System Developed for *AMedP-8*(*C*) for HD Inhaled Vapour Clinical Presentation 5

Time Point (hr)	Respiratory	Upper GI
1	0	1
4	1	2
18	2	2
24	3	2
48	3	1
72	4[a]	1
720		0

[a] According to the default value for $T_{death\text{-}CN\text{-}SL4}$, death would be modeled at this point.

Table 53. Symptom Progressions by Physiological System Developed for *AMedP-8*(*C*) for HD Inhaled Vapour Clinical Presentation 6

Time Point (hr)	Respiratory	Upper GI
1	0	1
4	1	2
18	2	2
24	3	2
48	4[a]	1
720		0

[a] According to the default value for $T_{death\text{-}CN\text{-}SL4}$, death would be modeled at this point.

Table 54. Symptom Progressions Developed for *AMedP-8*(*C*) for HD Ocular Symptoms

Time Point (hr)	Clinical Presentation #				
	1	**2**	**3**	**4**	**5**
1	0	0	0	0	0
2	0	0	0	0	1
3	0	0	0	1	2
4	0	0	1	2	2
5	0	1	1	2	2
6	0	1	2	2	2
9	1	1	2	2	2
11	1	1	2	2	3
12	1	2	2	3	3
18	2	2	2	[3]	3
36	1	2	2	3	3
60	0	1	2	3	3
108	0	0	2	3	3
168	0	0	2	2	2
504	0	0	1	1	1
672	0	0	0	0	0

Table 55. Symptom Progressions Developed for *AMedP-8*(*C*) for HD Equivalent Percutaneous Vapour Skin Symptoms

Time Point (hr)	Clinical Presentation		
	1	**2**	**3**
1	0	0	0
2	0	0	1
5	0	0	2
18	0	1	2
24	0	1	3
36	1	1	3
96	0	1	3
168	0	0	3
504	0	0	1
588	0	0	0

Table 56. Symptom Progression Developed for *AMedP-8*(*C*) for Liquid HD Clinical Presentation 1

Time Point (hr)	Respiratory
1	0
24	3
168	4
336	4[a]

[a] According to the SMEs at the chemical human response review, death would be modeled at this point.

AMedP-8(*C*) Injury Profiles

The symptom progressions provide the foundation for the Injury Profiles, which illustrate the effect of the injury on the body overall by tracking the highest severity level across the various physiological systems at any moment in time. The inhaled HD vapor Injury Profiles are shown in Table 57 and were created by combining the respiratory and upper GI symptom progressions. Because the Injury Profiles for the other routes of exposure (ocular vapor, equivalent percutaneous vapor, and percutaneous liquid) each comprised only one physiological system, these Injury Profiles are equivalent to the corresponding symptom progressions described in Table 54 through Table 56. They are repeated below in Table 58 through Table 60 independent of any physiological system.

Table 57. Inhaled HD Vapour Injury Profiles Developed for *AMedP-8*(*C*)

	Injury Profile					
Time Point (hr)	1	2	3	4	5	6
1	0	0	0	1	1	1
4	0	0	0	1	2	2
6	0	1	1	2	2	2
8	1	1	1	2	2	2
20	0	1	1	2	2	2
24	0	1	1	2	3	3
36	0	1	2	3	3	3
48	0	1	2	3	3	4[a]
72	0	1	2	3	4[a]	
168	0	0	2	3		
336	0	0	1	2		
720	0	0	0	1		
1008	0	0	0	0		

[a] According to the SMEs at the chemical human response review, death would be modeled at this point.

Table 58. Ocular HD Vapour Injury Profiles Developed for *AMedP-8*(*C*)

Time Point (hr)	Injury Profile				
	1	**2**	**3**	**4**	**5**
1	0	0	0	0	0
2	0	0	0	0	1
3	0	0	0	1	2
4	0	0	1	2	2
5	0	1	1	2	2
6	0	1	2	2	2
9	1	1	2	2	2
11	1	1	2	2	3
12	1	2	2	3	3
18	2	2	2	[3]	3
36	1	2	2	3	3
60	0	1	2	3	3
108	0	0	2	3	3
168	0	0	2	2	2
504	0	0	1	1	1
672	0	0	0	0	0

Table 59. Equivalent Percutaneous HD Vapour Injury Profiles Developed for *AMedP-8*(*C*)

Time Point (hr)	Injury Profile		
	1	**2**	**3**
1	0	0	0
2	0	0	1
5	0	0	2
18	0	1	2
24	0	1	3
36	1	1	3
96	0	1	3
168	0	0	3
504	0	0	1
588	0	0	0

Table 60. Liquid HD Injury Profile Developed for *AMedP-8*(*C*)

Time Point (hr)	Respiratory
1	0
24	3
168	4
336	4[a]

[a] According to the SMEs at the chemical human response review, death would be modeled at this point.

AMedP-7.5 Injury Profiles

As used in *AMedP-8*(*C*), each of the Injury Profiles shown in Table 57 through Table 60 was associated with a specific range of concentration times or doses. Likewise, in *AMedP-8*(*C*), all individuals with a given challenge were modeled to have the same response, which was described by the Injury Profile corresponding to the range spanning that challenge value. To allow for a more realistic estimate of the total number of casualties, the deterministic dose/concentration-time-based assignment of Injury Profiles from *AMedP-8*(*C*) was replaced in *AMedP-7.5* with a probabilistic probit-based assignment of individuals into Injury Profiles.

Rather than basing the Injury Profiles solely on challenge ranges, Injury Profiles in *AMedP-7.5* are specific to their maximum Injury Severity Level (mild, moderate, severe, or very severe). All six inhaled HD Injury Profiles developed for *AMedP-8*(*C*) were retained for use in *AMedP-7.5* and are shown in Table 61. Even though both *AMedP-8*(*C*) presentation 1 and presentation 2 (from Table 57) peaked at mild symptoms, they differed significantly on when symptoms ended (on Day 1 vs after Day 7), so both were used to model mild inhaled HD symptoms. For individuals modeled to experience symptoms peaking at mild severity, the determination of which mild Injury Profile to follow was made using the boundary from the *AMedP-8*(*C*) challenge ranges. The challenge value separating the two mild inhaled HD Injury Profiles in *AMedP-8*(*C*) was 70 mg-min/m^3 inhaled HD, so this was chosen as the dividing challenge for the *AMedP-7.5* Injury Profiles; individuals modeled to experience symptoms peaking at mild severity will follow inhaled HD Injury Profile presentation 1 if their challenge was less than 70 mg-min/m^3 and inhaled HD Injury Profile presentation 2 if their challenge was greater than or equal to 70 mg-min/m^3. As *AMedP-8*(*C*) inhaled HD Injury Profile presentation 3 was the only one to peak at moderate symptoms, this was used as the moderate inhaled HD Injury Profile in *AMedP-7.5*. Likewise *AMedP-8*(*C*) inhaled HD Injury Profile presentation 4 was used as the severe HD Injury Profile in *AMedP-7.5* because it was the only Injury Profile with symptoms peaking at Injury Severity Level 3 (“severe”). Finally, *AMedP-8*(*C*) inhaled HD Injury Profile presentations 5 and 6, both of which reached very severe symptoms, were both retained as very severe HD Injury Profiles in *AMedP-7.5*. As with the two mild Injury Profiles, the challenge value separating the Injury Profiles in *AMedP-8*(*C*) was used to determine which

Injury Profile individuals are modeled to follow in *AMedP-7.5*. Individuals modeled to experience very severe symptoms will follow *AMedP-8*(*C*) inhaled HD Injury Profile presentation 5 if their challenge was less than 1,200 mg-min/m^3 and *AMedP-8*(*C*) inhaled HD Injury Profile presentation 6 if their challenge was greater than or equal to 1,200 mg-min/m^3. These Injury Profiles were left distinct because they ended in death at different times (72 and 48 hours after exposure, respectively).

Table 61. *AMedP-7.5* Inhaled HD Injury Profiles

Time Point (hr)	Injury Profile					
	Mild, $X^{eff}_{HD,ih,n} < 70$	Mild, $X^{eff}_{HD,ih,n} \geq 70$	Moderate	Severe	Very Severe, $X^{eff}_{HD,ih,n} < 1200$	Very Severe, $X^{eff}_{HD,ih,n} \geq 1200$
1	0	0	0	1	1	1
4	0	0	0	1	2	2
6	0	1	1	2	2	2
8	1	1	1	2	2	2
20	0	1	1	2	2	2
24	0	1	1	2	3	3
36	0	1	2	3	3	3
48	0	1	2	3	3	4[a]
72	0	1	2	3	4[a]	
168	0	0	2	3		
336	0	0	1	2		
720	0	0	0	1		
1008	0	0	0	0		

[a] According to the default value for $T_{death\text{-}CN\text{-}SL4}$, death would be modeled at this point.

For the *AMedP-7.5* ocular HD vapor Injury Profiles, shown in Table 62, there is no mild Injury Profile, because none of the *AMedP-8*(*C*) Injury Profiles peaked at mild symptoms. Three Injury Profiles peaked at moderate symptoms, and there were operationally significant differences between all of them, so all were retained in *AMedP-7.5*. As with the inhaled HD Injury Profiles, the challenge range boundaries that originally defined the Injury Profiles in *AMedP-8*(*C*) were used to assign individuals to particular moderate Injury Profiles as a function of their challenge. Individuals exposed to ocular challenges of less than 26 mg-min/m^3 are modeled in *AMedP-7.5* to follow *AMedP-8*(*C*) ocular HD vapor Injury Profile presentation 1. Those exposed to ocular challenges between 26 and 50 mg-min/m^3 are modeled in *AMedP-7.5* to follow *AMedP-8*(*C*) ocular HD vapor Injury Profile presentation 2. Those exposed to ocular challenges greater than or equal to 50 mg-min/m^3 are modeled in *AMedP-7.5* to follow *AMedP-8*(*C*) ocular HD vapor Injury Profile presentation 3. *AMedP-8*(*C*) ocular HD vapor Injury Profile presentations 4 and 5 both reached their peak symptom severity ("severe") on Day 1 and are identical beginning

at 12 hours post-exposure. Because there was no operationally significant difference between them, only presentation 4 was retained in *AMedP-7.5*, and this was used as the severe ocular HD vapor Injury Profile. Because ocular symptoms cannot exceed severity level 3 ("severe"), there is no very severe ocular HD vapor Injury Profile in *AMedP-7.5*.

Table 62. *AMedP-7.5* Ocular HD Vapour Injury Profiles

Time Point (hr)	Injury Profile			
	Moderate $X^{eff}_{HD,oc} < 26$	Moderate $X^{eff}_{HD,oc} \geq 26$ and < 50	Moderate $X^{eff}_{HD,oc} \geq 50$	Severe
1	0	0	0	0
3	0	0	0	1
4	0	0	1	2
5	0	1	1	2
6	0	1	2	2
9	1	1	2	2
12	1	2	2	3
18	2	2	2	3
36	1	2	2	3
60	0	1	2	3
108	0	0	2	3
168	0	0	2	2
504	0	0	1	1
672	0	0	0	0

Similarly, the *AMedP-8*(*C*) equivalent percutaneous HD Injury Profiles were used in *AMedP-7.5* when possible. *AMedP-8*(*C*) equivalent percutaneous HD Injury Profile presentations 1 and 2 both peaked at mild symptoms, but days of onset and dissipation of the symptoms differed, so both were retained in *AMedP-7.5*. The challenge range boundary between the *AMedP-8*(*C*) Injury Profiles, 125 mg-min/m^3, was used to determine which Injury Profile individuals follow: *AMedP-8*(*C*) equivalent percutaneous HD Injury Profile presentation 1 for challenges below that boundary and *AMedP-8*(*C*) equivalent percutaneous HD Injury Profile presentation 2 for challenges greater than or equal to that value. There was no Injury Profile resulting in symptoms that peaked at moderate severity, so there is no *AMedP-7.5* moderate equivalent percutaneous HD Injury Profile. The *AMedP-8*(*C*) equivalent percutaneous HD Injury Profile, which peaked at severity level 3 symptoms, was used for the *AMedP-7.5* severe equivalent percutaneous HD Injury Profile. Rather than retain percutaneous liquid as a fourth route of exposure associated with only a single Injury Profile, the *AMedP-8*(*C*) liquid HD Injury Profile was used in *AMedP-7.5* as a very severe equivalent percutaneous HD vapor Injury Profile. The cause of the bone

marrow suppression that is modeled to lead to sepsis and death is described as systemic absorption of HD, indicating that the amount of HD in systemic circulation, rather than the source of the challenge (liquid vs vapor), determines the human response.[135] Thus, individuals challenged with lethal doses of liquid HD would still be modeled to die at 336 hours, but the challenge would first be converted to the equivalent percutaneous HD vapor using the conversion factor derived from *AMedP-7.5* Equation 4-22. All *AMedP-7.5* equivalent percutaneous HD vapor Injury Profiles are shown in Table 63.

Table 63. *AMedP-7.5* Equivalent Percutaneous HD Vapour Injury Profiles

Time Point (hr)	Injury Profile			
	Mild $X^{eff}_{HD,epc} < 125$	Mild $X^{eff}_{HD,epc} \geq 125$	Severe	Very Severe
1	0	0	0	0
2	0	0	1	1
5	0	0	2	2
18	0	1	2	2
24	0	1	3	3
36	1	1	3	3
96	0	1	3	3
168	0	0	3	3
336	0	0	3	4[a]
504	0	0	1	
588	0	0	0	

[a] Death is modeled at this point, regardless of the values of the various methodology parameters.

Toxicity Parameters (*AMedP-7.5 Tables 4-19, 4-21, and 4-23*)

15. Best Available HD Toxicity Values

Table 64 lists the HD toxicity parameter values that were used in *AMedP-7.5*. Although we consulted several other sources (NATO doctrine, HPAC, and recent research published in open literature such as journals) in search of parameter values, we found that the few sources that actually provide parameter values tend to use the same values as FM 3-11.9[136] (whether directly cited or not). Thus, the FM 3-11.9 values are simply presented in Table 64.

135 USAMRICD, *Medical Management of Chemical Casualties*, 99–100; Hurst et al., "Vesicants," 290.

136 USACMLS, *Chemical/Biological Agents and Compounds*, II-40.

Table 64. HD Toxicity Values

Challenge Route	Parameter	Value	Applicable Temperature
Ocular Vapour	$ECt_{50\text{-mild}}$	25 mg-min/m^3	All
	PS_{mild}	3 probits/log (dose)	All
	$ECt_{50\text{-severe}}$	75 mg-min/m^3	All
	PS_{severe}	3 probits/log (dose)	All
Inhaled Vapour	LCt_{50}	1,000 mg-min/m^3	All
	PS_{lethal}	6 probits/log (dose)	All
Percutaneous Vapour	$ECt_{50\text{-mild}}$	50 mg-min/m^3 25 mg-min/m^3	18.33 – 29.44 °C (65–85 °F) > 29.44 °C (> 85 °F)
	PS_{mild}	3 probits/log (dose)	All
	$ECt_{50\text{-severe}}$	500 mg-min/m^3 200 mg-min/m^3	18.33 – 29.44 °C (65–85 °F) > 29.44 °C (> 85 °F)
	PS_{severe}	3 probits/log (dose)	All
	LCt_{50}	10,000 mg-min/m^3 5000 mg-min/m^3	18.33 – 29.44 °C (65–85 °F) > 29.44 °C (> 85 °F)
	PS_{lethal}	7 probits/log (dose)	All
Percutaneous Liquid	$ED_{50\text{-severe}}$	600 mg	All
	PS_{severe}	3 probits/log (dose)	All
	LD_{50}	1,400 mg	All
	PS_{lethal}	7 probits/log (dose)	All

Note: The source for all toxicity values in Table 64 is FM 3-11.9, II-40.

Extrapolation of HD Toxicity Values

Correctly allocating individuals among the HD Injury Profiles requires that for each Injury Profile and associated challenge route, there is a probit model that describes the likelihood of manifesting symptoms at least as severe as the peak symptoms for that Injury Profile. For the ocular HD vapor Injury Profiles, the severe ocular vapor toxicity parameters from Table 64 were used directly for the severe Injury Profile. Since mild symptoms were modeled to progress to moderate symptoms in all ocular HD vapor Injury Profiles, the probability of developing at least mild symptoms was the same as the probability of developing at least moderate symptoms, and the mild ocular vapor toxicity parameters from Table 64 were used for the moderate Injury Profiles.

The mild, severe, and lethal percutaneous HD vapor toxicity parameters from Table 64 were used for the mild, severe, and very severe equivalent percutaneous HD vapor Injury Profiles, respectively.

For the inhaled HD vapor Injury Profiles, only the very severe Injury Profile could be associated directly with toxicity parameters from the literature (the lethal inhaled HD vapor toxicity parameters from Table 64). For the other Injury Profiles, we needed to extrapolate mild, moderate, and severe probit model parameter values from the lethal toxicity values and the *AMedP-8*(*C*) dosage ranges.

Although it is difficult to determine and define the mechanism(s) of HD injury, we have no reason to believe that the mechanism changes substantially between mild, moderate, severe, and lethal inhalation effects, so we assumed that the probit slopes for all inhaled HD vapor effects levels were equal to the lethal probit slope, 6 probits/log (dose).[137] The assumption also helps avoid illogical results such as two toxicity curves intersecting. Given a probit slope, any point on the probit curve will specify the model, and the corresponding ECt_{50} value can be calculated.

For the mild inhaled HD vapor Injury Profiles, the lower bound of the *AMedP-8*(*C*) inhaled HD vapor Injury Profile for clinical presentation 1 (see Table 57) was assumed to be equal to the $ECt_{16\text{-mild}}$. This Injury Profile is the least severe Injury Profile from *AMedP-8*(*C*) that resulted in mild symptoms and originally corresponded to 50–70 mg-min/m^3 inhaled HD. Therefore, the inhaled HD vapor $ECt_{16\text{-mild}}$ was assumed equal to 50 mg-min/m^3. Given the $ECt_{16\text{-mild}}$ and the probit slope, *AMedP-7*.5 Equation 4-1 was used to solve for the $ECt_{50\text{-mild}}$. As shown in the calculations below, the inhaled HD vapor $ECt_{50\text{-mild}}$ value was calculated to be 73 mg-min/m^3:

$$p_{Q\_k,n} = \Phi\left(PS_{Q\_k} \cdot \log_{10}\left(\frac{X_{Q,n}^{eff}}{ECt_{50,Q\_k}}\right)\right)$$

$$0.16 = \Phi\left(6 \cdot \log_{10}\left(\frac{50}{ECt_{50,HD,ih\_mild}}\right)\right)$$

$$ECt_{50,HD,ih\_mild} = 73$$

Similarly, the lower bound of the *AMedP-8*(*C*) inhaled HD vapor Injury Profile for clinical presentation 3, the least severe Injury Profile with moderate symptoms (see Table 57), was assumed to be equal to the $ECt_{16\text{-moderate}}$. This Injury Profile was associated with a challenge range of 100–150 mg-min/m^3 inhaled HD in *AMedP-8*(*C*), so the inhaled

137 This principle is applied for several agents in Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*.

HD vapor $ECt_{16\text{-moderate}}$ was assumed equal to 100 mg-min/m^3. Using *AMedP-7.*5 Equation 4-1, the inhaled HD vapor $ECt_{50\text{-moderate}}$ was calculated to be 146 mg-min/m^3:

$$p_{Q\_k,n} = \Phi\left(PS_{Q\_k} \cdot \log_{10}\left(\frac{X_{Q,n}^{eff}}{ECt_{50,Q\_k}}\right)\right)$$

$$0.16 = \Phi\left(6 \cdot \log_{10}\left(\frac{100}{ECt_{50,HD,ih\_moderate}}\right)\right)$$

$$ECt_{50,HD,ih\_moderate} = 146$$

In the same way, the lower bound of the *AMedP-8*(*C*) inhaled HD vapor Injury Profile for clinical presentation 4, the least severe Injury Profile with severe symptoms (see Table 57), was assumed to be equal to the $ECt_{16\text{-severe}}$. This Injury Profile was associated with a challenge range of 150–250 mg-min/m^3 inhaled HD in *AMedP-8*(*C*), so the inhaled HD vapor $ECt_{16\text{-severe}}$ was assumed equal to 150 mg-min/m^3. Using *AMedP-7.*5 Equation 4-1, the inhaled HD vapor $ECt_{50\text{-severe}}$ was calculated to be 220 mg-min/m^3:

$$p_{Q\_k,n} = \Phi\left(PS_{Q\_k} \cdot \log_{10}\left(\frac{X_{Q,n}^{eff}}{ECt_{50,Q\_k}}\right)\right)$$

$$0.16 = \Phi\left(6 \cdot \log_{10}\left(\frac{150}{ECt_{50,HD,ih\_severe}}\right)\right)$$

$$ECt_{50,HD,ih\_severe} = 220$$

Table 65. Extrapolated Inhaled HD Vapour Toxicity Values Used in *AMedP-7.5*

Parameter	Value
$ECt_{50\text{-mild}}$	73 mg-min/m^3
PS_{mild}	6 probits/log (dose)
$ECt_{50\text{-moderate}}$	146 mg-min/m^3
$PS_{moderate}$	6 probits/log (dose)
$ECt_{50\text{-severe}}$	220 mg-min/m^3
PS_{severe}	6 probits/log (dose)

A final caveat related to the extrapolated toxicity parameters is that we do not recommend they be used for any purpose other than casualty estimates within *AMedP-7.5*, and if estimates for these parameters become available from toxicity experts such as ECBC, CSAC, USAMRICD, Porton Down, or any other well-qualified laboratory in a NATO country, we recommend that the experts' estimates be adopted instead in the next version of *AMedP-7.5*.

Medical Treatment (*AMedP-7.5 Table 4-25*)

Efficacy of Medical Treatment

Although researchers around the world are developing concepts for medical countermeasures aimed at "elimination of body contact, improved decontamination, pharmacological intervention, and chemical casualty management,"[138] no antidote exists for HD exposure, and no uniform standards of care have been developed.[139] Treatment consists mainly of symptomatic and supportive care, although evidence from non-human primate studies has suggested that granulocyte colony-stimulating factor (G-CSF) may be effective at reducing the recovery period following HD-induced neutropenia.[140]

MTOR Table

To estimate the fractions of patients that RTD, CONV, and DOW over time, we conducted a thorough investigation of data sources. Although it is estimated that 1,200,000 soldiers were exposed to HD throughout WWI, of which 400,000 required prolonged medical attention,[141] adequate information on treatment time and hospital discharge was scarce. The best account of the effects of treatment on mortality and the duration of hospitalization was Willems' description of 65 Iranian HD patients evaluated in European hospitals after medical evacuation from the Iran-Iraq War.[142] This dataset provides information on the cause of death for those casualties that did not survive, as well as the time until discharge from the hospital for those that survived. Limitations on the dataset included symptom descriptions at the group (rather than individual) level, unknown dosages, missing hospital admittance or discharge dates, unequal distribution of casualties among Injury Profile cohorts, and varying patient admission dates ranging from 4 to 17 days after exposure.[143] Table 66 (reproduced from Willems' Table II-1) shows the total duration of hospitalization for each of the 65 HD patients.[144] Note that a 66th patient in the Willems report was excluded from Table 66 because he was determined to not be a chemical casualty.

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138 John S. Graham et al., "Wound Healing of Cutaneous Sulfur Mustard Injuries: Strategies for the Development of Improved Therapies," *Journal of Burns and Wounds* 4 (2009): 10.

139 Hurst et al., "Vesicants," 278. 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.

140 Dana R. Anderson et al., "Sulfur Mustard-Induced Neutropenia: Treatment with Granulocyte Colony-Stimulating Factor," *Military Medicine* 171, no. 5 (2006): 448–453.

141 Mahdi Balali-Mood and Mehrdad Hefazi, "The Pharmacology, Toxicology, and Medical Treatment of Sulphur Mustard Poisoning," *Fundamental & Clinical Pharmacology* 19 (2005): 298.

142 Jan L. Willems, "Clinical Management of Mustard Gas Casualties," *Annales Mediciniae Militaris Belgicae* 3, no. suppl 1 (1989).

143 Ibid.

144 Ibid., 4–5.

Table 66. Time Post-Exposure until Discharge from European Hospital or Death for 65 Iranian Mustard Casualties

Index	Days to Discharge	Days to Death	Index	Days to Discharge	Days to Death	Index	Days to Discharge	Days to Death
1	27		23	71		45	17	
2		12	24	41		46	25	
3		16	25	26		47	34	
4	21		26	76		48	69	
5		13	27	26		49	54	
6	22		28	48		50	69	
7	33		29	34		51	51	
8	33		30	43		52	40	
9	28		31	42		53	45	
10		185	32	38		54	50	
11	28		33	38		55	45	
12	21		34	41		56	50	
13	41		35	39		57	66	
14	42		36	27		58		7
15		15	37	34		59	52	
16	47		38	27		60	Unknown	
17	36		39	39		61		Unknown
18	47		40		12	62	Unknown	
19	36		41	50		63	Unknown	
20	26		42	50		64	28	
21	26		43	43		65	28	
22		6	44	26				

The recovery descriptions from the Iranian casualties and other historical cases from the literature formed the basis for the estimated distributions of time until DOW/RTD/CONV for each Injury Profile cohort. We used the Iranian patient discharge times in Table 66 to estimate the duration of treatment only for the EPC Injury Profile cohorts, because "the duration of the hospital stay was mainly determined by the healing time of the skin lesions."[145] Other Injury Profile cohort distributions were estimated using summaries of the injury-specific treatment durations provided by Willems and other sources.

Only individuals categorized as EPC Very Severe, IH Very Severe, $X^{eff}_{HD,ih} < 1200$, or IH Very Severe, $X^{eff}_{HD,ih} \geq 1200$ are modeled to DOW. For the majority of the remaining Injury Profile cohorts, hospital discharge is modeled to coincide with reaching

145 Ibid., 48.

Convalescence, not RTD, because a review of historical HD cases indicates that RTD is likely only for the mildest cases. Regarding inhalation injuries, MACW warns, "Only those individuals experiencing irritation without significant tissue injury will be able to return to duty…Those with severe cases may never return to duty."[146] Referring to ocular exposures, MACW prescribes, "Patients with only the mildest eye irritations to sulfur mustard, those requiring only soothing eye drops, will be able to return to duty…Moderate conjunctivitis may require a 2-month recovery before return to duty is possible."[147] Finally, on the topic of percutaneous cases, MACW asserts, "Only patients with small TBSA [total body surface area] injuries (less than 5%) in noncritical areas will be able to return to duty following treatment with topical antibiotic, dressings, and oral analgesics."[148] Therefore, AMedP-7.5 models RTD only for IH Mild (two distinct cohorts), OC Moderate, $X^{eff}_{HD,oc} < 26$ (the lowest Ocular cohort), and EPC Mild, $X^{eff}_{HD,epc} < 125$ (the lowest Equivalent Percutaneous cohort); all others that do not DOW are modeled to become convalescent (CONV) indefinitely. Below, by Injury Profile cohort, we describe the medical treatment parameters used in AMedP-7.5. Table 67 summarizes the medical treatment outcome reporting for all HD Injury Profiles.

IH Mild, $X^{eff}_{HD,ih} < 70$

Untreated, mild inhaled HD symptoms are modeled to resolve after 20 hours based on the Injury Profile (see Table 61). Even if treatment expedited the recovery time, patients would still be reported as WIA on Day 1 and RTD on Day 2. Therefore, 100% of patients are modeled to RTD on Day 2 with treatment.

IH Mild, $X^{eff}_{HD,ih} \geq 70$

As specified in the Injury Profile (Table 61), symptoms for individuals in this Injury Profile cohort are modeled to last 168 hours (7 days) without treatment, so patients would be modeled to RTD on Day 8 untreated. To model the beneficial effects of treatment, patients in this Injury Profile cohort are modeled to RTD according to a uniform distribution with equal probability (1/5 = 20%) on each of Days 4 through 8, reflecting the variation in response to treatment and the *MACW* comment that "determining the level of [lung] injury requires observation for 3 to 7 days."[149]

IH Moderate and IH Severe

Untreated, symptoms for individuals in the IH Moderate and IH Severe Injury Profile cohorts are modeled to resolve after 30 and 42 days, respectively (see Table 61). For 14 patients described by Willems that developed secondary lung lesions but did not require

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146 Hurst et al., "Vesicants," 290–291.

147 Ibid., 290.

148 Ibid., 291.

149 Ibid., 291.

artificial ventilation, lung infection resolved 9 to 30 days after exposure.[150] We judged these individuals to be representative of the IH Moderate and IH Severe Injury Profile cohorts because symptoms resolved sooner than when untreated but later than the treated IH Mild, $X^{eff}_{HD,ih} \geq 70$ Injury Profile symptoms (8 days). In addition, the individuals in Willems's report with more severe respiratory injuries required artificial respiration and likely correspond to the IH Very Severe Injury Profile cohorts.

Although Balali-Mood and Hefazi report that "some irritation, cough and huskiness may persist for as long as 6 weeks"[151] following an infection of the respiratory tract, the lung infections for all the patients described by Willems, even the patient surviving only with artificial ventilation, had resolved by the end of the fifth week.[152] By looking at the time distribution of the end of infection for the 14 patients not requiring ventilatory support, we can see that the distribution is not uniform. Assuming individuals transition from WIA to CONV the day after the infection cleared, the weekly distribution of individuals convalescing in this group is as follows: Week 2, 3 individuals; Week 3, 8 individuals; Week 4, 1 individual; and Week 5, 2 individuals.

Based on this distribution, treated individuals in the IH Moderate Injury Profile cohort are modeled to transition from WIA to CONV in Weeks 2 and 3, and those in the IH Severe cohort are modeled to transition in Weeks 4 and 5. For the IH Moderate Injury Profile cohort, 3/11 (≈ 27%) of individuals are reported as CONV by Day 14 (3/11 ÷ 6 ≈ 4.5% on each of Days 9 through 14) and 8/11 (≈ 73%) are reported by Day 21 (8/11 ÷ 7 ≈ 10.4% on each of Days 15 through 21). For the IH Severe Injury Profile cohort, since there are only three data points, the transition from WIA to CONV is assumed to be uniformly distributed across Weeks 4 and 5. Therefore, *AMedP-7.5* reports 50% of individuals in this cohort to CONV by Day 28 and the remaining 50% by Day 35 (1/14 ≈ 7.1% on each of Days 22 through 35).

IH Very Severe, $X^{eff}_{HD,ih} < 1200$

Eight cases from the Willems report required artificial ventilation, seven of whom died despite ventilatory support.[153] One of those individuals died at an unknown time, one died 185 days after exposure (and his time to death is considered an outlier), and the other five died 6 to 16 days after exposure,[154] timelines consistent with Balali-Mood and Hefazi's claim that death following infection of the respiratory tract and bronchopneumonia may

150 Willems, "Clinical management," 45, Table IV-7.

151 Balali-Mood and Hefazi, "Pharmacology, Toxicology, and Medical Treatment," 301.

152 Willems, "Clinical management," 45–46, Table IV-7, Table IV-8.

153 Ibid., 46, Table IV-8.

154 Ibid.

occur "at any time between the second day and the fourth week."[155] *AMedP-7.5* models untreated individuals in this cohort to die after 72 hours (3 days) and reports them as DOW on Day 4. With treatment, 87.5% (7/8) of individuals in this Injury Profile cohort are reported as DOW with equal probability (1/25 = 4%) on Days 4 through 28. The 12.5% (1/8) of individuals in this cohort that are modeled to survive remain in the hospital until the end of Week 5, the same duration as the longest hospital stays for the IH Severe Injury Profile cohort. Therefore, 12.5% of individuals in this Injury Profile cohort are reported as CONV on Day 35 and 3.5% (4% × 87.5%) are reported to DOW on each of Days 4 through 28. Aggregating the DOWs by week, this would be reported as 14% on Day 7 and 24.5% each on Days 14, 21, and 28.

IH Very Severe, $X^{eff}_{HD,ih} \geq 1200$

Untreated individuals in this cohort are modeled to die after 48 hours (2 days). They would thus be reported as DOW on Day 3. Even with treatment, individuals in this cohort are modeled to DOW on Day 3, because severe bronchopneumonia from such a high dose could cause them to die as soon as the second day.[156]

OC Moderate, $X^{eff}_{HD,oc} < 26$

Untreated symptoms for this cohort are modeled to resolve after 60 hours (see Table 62). Although ointments and creams applied to the eyes may reduce the pain, they may not restore vision in all cases. According to *MACW*, "patients with only the mildest eye irritations to sulfur mustard, those requiring only soothing eye drops, will be able to return to duty."[157] Because this is the least severe ocular Injury Profile, only individuals in this cohort will be modeled to RTD; all other Injury Profile cohorts will be modeled to transition from WIA to CONV or DOW. To reflect the variability in the effects of treatment for this cohort, 50% of individuals in this cohort will be modeled to RTD on Day 2 (the earliest RTD can be modeled) and 50% will be modeled to RTD on Day 3 (reflecting at least half a day improvement on recovery time over the untreated case).

a. OC Moderate, $X^{eff}_{HD,oc} \geq 26$ and < 50, OC Moderate, $X^{eff}_{HD,oc} \geq 50$, and OC Severe

Willems described both the treatment duration and the complete healing times for the ocular injuries in the Iranian patients as follows.

> Eye treatment lasted between 3 and 28 days, after which complete healing was obtained in most cases, although there was still some photophobia at the time of discharge from the hospital. In four cases keratitis punctate, i.e., the presence of small epithelial defects of the cornea, was diagnosed

[155] Balali-Mood and Hefazi, "Pharmacology, Toxicology, and Medical Treatment," 301.

[156] Ibid.

[157] Hurst et al., "Vesicants," 290.

> clinically and confirmed by slit-lamp biomicroscopy after hospital stays of 21 (patient N5), 28 (patient N4), 66 (patient D2) and 71 (patient D7) days. Patients N6-N10 still had some infiltration of the corneal epithelium, at the level of the eyelid cleft, when they left the hospital 46 to 60 days after exposure. Patient N2 had a temporal symblepharon at the right eye.
>
> This clinical course is in agreement with previous observations: healing times of 2 weeks for mild conjunctivitis, 4–5 weeks for severe conjunctivitis, and 2–3 months for corneal lesions.[158]

MACW describes nearly the same time ranges for complete recovery from mild conjunctivitis (1 to 2 weeks), severe conjunctivitis (2 to 5 weeks), and corneal erosion (2 to 3 months).[159] These three clinical courses parallel the OC Moderate, $X^{eff}_{HD,oc} \geq 26$ and < 50; OC Moderate, $X^{eff}_{HD,oc} \geq 50$; and OC Severe Injury Profiles, respectively.

When modeling treatment for HD casualties in *AMedP-7.5*, we made the following assumptions. First, patients should not be modeled to remain WIA for longer periods of time in the treated case than the untreated case (i.e., treatment should not prolong casualty status for survivors). Second, after the resolution of ocular treatment (assuming all other symptoms have resolved), patients could be managed via convalescent care until they fully recover.

Without treatment, the symptoms of individuals in these ocular Injury Profile cohorts are modeled to resolve after 4.5 days (for the OC Moderate, $X^{eff}_{HD,oc} \geq 26$ and < 50 cohort) and 28 days (for the OC Moderate, $X^{eff}_{HD,oc} \geq 50$ and OC Severe cohorts). With treatment, individuals are modeled to become CONV on Days 4 through 28 (roughly corresponding to the duration of treatment described by Willems) and may not fully recover until the times described above. Of the individuals in the OC Moderate, $X^{eff}_{HD,oc} \geq 26$ and < 50 cohort, 50% are modeled to become CONV on Day 4 and the remaining 50% on Day 5. *AMedP-7.5* models individuals in the OC Moderate, $X^{eff}_{HD,oc} \geq 50$ cohort to become CONV with equal probability ($1/9 \approx 11\%$) on each of Days 6 through 14. Aggregating by week, this would be reported as 22% on Day 7 and 78% on Day 14. Last, individuals in the OC Severe cohort are modeled to become CONV with equal probability ($1/14 \approx 7\%$) on each of Days 15 through 28. Aggregating by week, this would be reported as 50% on Day 21 and 50% on 28.

EPC Mild $X^{eff}_{HD,epc} < 125$

Untreated symptoms for this cohort are modeled to resolve after 4 days (Table 63), and individuals are modeled to RTD on Day 5. With treatment, individuals in this cohort are modeled to RTD with equal probability ($1/3 \approx 33\%$) on each of Days 3, 4, and 5.

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158 Willems, "Clinical management," 40.

159 Hurst et al., "Vesicants," 274.

EPC Mild $X^{eff}_{HD,epc} \geq 125$

Without treatment, symptoms are modeled to resolve after 7 days (see Table 63). With treatment, individuals are modeled to transition from WIA to CONV with equal probability (1/3 ≈ 33%) on each of Days 6, 7, and 8.

EPC Severe

Symptoms in this Injury Profile are modeled to resolve after 24.5 days without treatment. Of the Iranian casualties, four were discharged before Day 25 (on Days 17, 21, 21, and 22). Assuming these individuals are representative of the EPC Severe Injury Profile cohort and that no patients in this cohort enter CONV before the third week after exposure, we modeled individuals to transition from WIA to CONV with equal probability (1/11 ≈ 9%) on each of Days 15 through 25. By week, this would be reported as 64% at the end of Week 3 and 36% at the end of Week 4.

EPC Very Severe

It is difficult to separate the contributions of various routes of exposure to the deaths of the fatal Iranian HD casualties described by Willems: "one with acute airway obstruction (N11), one with septicemia and shock (A2), two with lung pathology (B5, P2), and five with lung pathology, septicemia and shock (A3, A5, C1, D3 and K1)."[160] The seven fatalities with lung pathology were used to estimate the likelihood of dying following inhalation of HD vapor (see the section above on IH Very Severe, $X^{eff}_{HD,ih} < 1200$). For patients A2 and N11, death was likely caused by percutaneous absorption of liquid or vapor HD and the subsequent bone marrow depression, because both suffered from leukopenia and septicemia, died without recovery of the leukopenia, and exhibited no evidence of lung pathology.[161] A case could also be made that this route of exposure contributed to the deaths of patients A3, A5, C1, D3 and K1, because they too were leukopenic, septicemic, and suffering cardiovascular shock until their deaths (except for A3, who recovered from his leukopenia on the day of his death). However, because it would be impossible to know whether these individuals would have died from their percutaneous exposures had they not succumbed to their inhalation-induced injuries, they have been excluded from the estimation of the EPC Very Severe cohort treatment duration and case fatality rate.

Excluding the individuals that experienced lung pathology, there were 23 individuals that were reported to have leukopenia and/or septicemia, 2 of whom died (a fatality rate of approximately 9%).[162] The fatalities, patients A2 and N11, died 12 and 7 days after exposure, respectively. The discharge dates for the 21 survivors are: 26, 27, 27, 27, 28, 28, 28, 33, 34, 36, 38, 38, 39, 40, 42, 45, 51, 52, and 76 days after exposure (and unknown for

160 Willems, "Clinical management," 47.

161 Ibid., 41–42, Table IV-2, Table IV-3.

162 Ibid., 41, Table IV-2.

patients P3 and P4).[163] Patient D7 (discharged on Day 76) was considered an outlier and was excluded from further analysis. The remaining 18 survivors with known discharge dates were grouped by week of discharge, and the weekly fractions of this cohort transitioning to CONV was smoothed to avoid overfitting the limited data.

For the sake of model simplicity and to employ round numbers that sum to 100%, we modeled the fraction of individuals estimated to die for this Injury Profile cohort as 8% (reported on Day 10, the approximate median of the two times to death), distributing the remaining 92% of individuals over Weeks 4 through 8. Thirty-six percent of these survivors are reported to transition from WIA to CONV on Day 28, and 14% are reported on each of Days 35, 42, 49, and 56.

[163] Ibid., 41, Table IV-2, 3–4, Table II-1.

Table 67. *AMedP-7.5* HD Medical Treatment Outcome Reporting

Injury Profile	DOW[a]	CONV[a]	RTD[a]
Inhalation Injury Profiles			
IH Mild, $X^{eff}_{HD,ih}$[b] < 70	0%	0%	Day 2: 100%
IH Mild, $X^{eff}_{HD,ih}$[b] ≥ 70	0%	0%	Day 4: 20% Day 5: 20% Day 6: 20% Day 7: 20% Day 8: 20%
IH Moderate	0%	Day 14: 27% Day 21: 73%	0%
IH Severe	0%	Day 28: 50% Day 35: 50%	0%
IH Very Severe, $X^{eff}_{HD,ih}$[b] < 1200	Day 7: 14% Day 14: 24.5% Day 21: 24.5% Day 28: 24.5%	Day 35: 12.5%	0%
IH Very Severe, $X^{eff}_{HD,ih}$[b] ≥ 1200	Day 3: 100%	0%	0%
Ocular Injury Profiles			
OC Moderate, $X^{eff}_{HD,oc}$[b] < 26	0%	0%	Day 2: 50% Day 3: 50%
OC Moderate, $X^{eff}_{HD,oc}$[b] ≥ 26 and < 50	0%	Day 4: 50% Day 5: 50%	0%
OC Moderate, $X^{eff}_{HD,oc}$[b] ≥ 50	0%	Day 7: 22% Day 14: 78%	0%
OC Severe	0%	Day 21: 50% Day 28: 50%	0%
Equivalent Percutaneous Injury Profiles			
EPC Mild, $X^{eff}_{HD,epc}$[b] < 125	0%	0%	Day 3: 33% Day 4: 33% Day 5: 34%
EPC Mild, $X^{eff}_{HD,epc}$[b] ≥ 125	0%	Day 6: 33% Day 7: 33% Day 8: 34%	0%
EPC Severe	0%	Day 21: 64% Day 28: 36%	0%
EPC Very Severe	Day 10: 8%	Day 28: 36% Day 35: 14% Day 42: 14% Day 49: 14% Day 56: 14%	0%

[a] Reported values indicate the fraction that changes status on a given day; they are not cumulative.

[b] $X^{eff}_{HD,Q}$ is the Effective CBRN Challenge (dosage) of HD for route of exposure Q.

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1.8. CG Model (*AMedP-7.5 Section 4.2.8*)

Introduction

Phosgene (CG) is a pulmonary chemical agent that was used during World War I (WWI)[164] and is now often referred to as a toxic industrial compound (TIC) because of its use in the chemical industry;[165] however, we refer to it as a chemical agent. As a pulmonary agent, CG's primary mechanism of injury is damage to the lung.

The objective of this chapter is to describe the human response model for CG as it has been incorporated into *AMedP-7.5*. The chapter first discusses a scoping assumption. Then it describes the physiological effects of CG, the toxicity parameters used in *AMedP-7.5*, development of Injury Profiles, and the medical treatment model.

Assumption (*AMedP-7.5 Section 4.2.8.2*)

> **Assumption**: Percutaneous exposure to CG vapour and liquid are negligible.

The percutaneous vapor is assumed negligible because in all the research performed in the development of this model, no sources were found that discussed CG injury resulting from percutaneous vapor exposure. Further, the liquid resulting from a CG attack, and thus the percutaneous liquid contribution to dose, may be neglected due to the agent's high volatility.[166] This assumption may result in an underestimate of the number and severity of casualties.

Physiological Effects[167] (*AMedP-7.5 Tables 4-26 and 4-28*)

CG is distinguished by its musty hay odor, the generalized mucous membrane irritation it causes immediately at relatively low concentrations, and the dyspnea and delayed (hours to days) pulmonary edema that it can cause after more significant exposure.

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164 Shirley D. Tuorinsky and Alfred M. Sciuto, "Toxic Inhalational Injury and Toxic Industrial Chemicals," chap. 10 in *Medical Aspects of Chemical Warfare*, ed. Shirley D. Tuorinsky, Textbooks of Military Medicine (Washington, DC: Office of the Surgeon General, Borden Institute, Walter Reed Army Medical Center, 2008), 342 (Table 10-2).

165 Ibid., 343 (Table 10-3).

166 USACMLS, *Chemical/Biological Agents and Compounds*, II-11.

167 This section is largely paraphrased from William D. Currie, *Attenuation of Phosgene Toxicity* (Durham, North Carolina: Duke University Medical Center, October 1995); Alfred M. Sciuto, "Inhalation Toxicology of Irritant Gas–Historical Perspectives, Current Research, and Case Studies of Phosgene Exposure," in *Inhalation Toxicology*, 2nd ed., ed. Harry Salem and Sidney A. Katz (Boca Raton, FL: CRC Press, 2006), 457–483; Jonathan Borak and Werner F. Diller, "Phosgene Exposure: Mechanisms of Injury and Treatment Strategies," *Journal of Occupational and Environmental Medicine* 43, no. 2 (2001): 110–119; National Research Council, "Phosgene: Acute Exposure Guideline Levels," appendix 1 of Vol. 2 of *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (Washington, DC: The National Academies Press, 2002).

CG is a highly reactive oxidant gas that when inhaled nonspecifically and irreversibly, acylates macromolecules in the functional portions of the lungs. CG also quickly hydrolyzes to hydrochloric acid (HCl) when it comes into contact with the moist membrane surfaces of the eye, nose, throat, and bronchi, to cause the initial irritation. The physiological mechanisms of non-HCl-related lung injury in response to inhaling CG are extremely complex, are not well understood, and have been subject to various competing hypotheses.

The literature is surprisingly vague and variable in its descriptions of the symptoms and injury progression. The most plausible explanation is that the symptomology does not lend itself to exact description. As stated by Diller, the "intensity of the reflex symptoms … varies greatly between individuals; moreover, it is not strictly proportional to the inhaled dose of phosgene and therefore permits no prognostic conclusions."[168] Clinical experience from WWI, which involved significant use of CG as a weapon, supports Diller's statement. For example, Vedder notes that in "Field Hospitals patients who present no serious symptoms on arrival may leave their beds to visit the latrine, and a moment after returning they may be taken with progressive dyspnea, which in the absence of immediate treatment may be followed by cyanosis and death."[169] Given this warning, it is important to remember that the correlations presented below are intended to represent the median individual. For CG, the variance around the median is perhaps higher than with other agents.

The effect of CG poisoning depends on concentration and dosage. At high *concentration*, CG immediately causes mild ocular and respiratory irritation because of the formation of HCl. The irritation quickly disappears after exposure ends. After the irritation symptoms, the person might recover completely. If the *dosage* was high enough, however, the person might progress from dyspnea to cough to pulmonary edema after an asymptomatic latent phase. The literature does not provide a description of an intermediate symptom complex (i.e., most victims either suffer relatively mild and transient effects or suffer (after a delay) life-threatening pulmonary edema). The lack of intermediate symptoms is consistent with clinical experience with CG casualties from WWI.[170]

The only other result of CG exposure mentioned in the literature is that at very high *concentrations*, CG can cause death within minutes. In summarizing WWI soldiers' experience with CG, Vedder stated that this situation was caused by the lung abruptly ceasing to function, resulting in shock and circulatory failure, but no specific concentration was mentioned in connection with this phenomenon—only "phosgene in concentrated

168 Werner F. Diller, "Pathogenesis of Phosgene Poisoning," *Toxicology and Industrial Health* 1, no. 2 (1985): 8.

169 Edward B. Vedder, "The Pulmonary Irritants—Chlorine, Phosgene, Chloropicrin," in *The Medical Aspects of Chemical Warfare* (Baltimore, MD: Williams & Wilkins Company, 1925), 89.

170 Ibid., 89–95.

form."[171] Borak and Diller proposed that the mechanism of death is CG passing through the blood-air barrier into the pulmonary circulatory system, causing hemolysis (rupture of red blood cells), which causes pulmonary blood flow to nearly cease within minutes. Victims die from acute overdistension of the right chamber of the heart.[172] Although Borak and Diller state a specific concentration that causes this phenomenon, they do not directly cite any data, and it seems that Diller's experience is based on experiments with rats.[173] Further, the claim has not been repeated in other sources (such as *MACW*), and there is no data on the concentration that would cause it to occur in humans. Finally, Vedder described a case in which a chemist accidentally inhaled "almost pure phosgene"[174] being used in a chemical synthesis and died about 6 hours later. Still, it seems that rapid death is not necessarily a rule. Although the rapid death phenomenon certainly happened in WWI, there is an insufficient basis for including it in the *AMedP-7.5* models, and it will not be discussed further.

Although there is consensus that inhalation of CG can cause pulmonary edema[175] (the major delayed (30 minutes to several days) clinical effect associated with CG poisoning), there is confusion regarding the mechanism by which it does so. In the period immediately after WWI (and still in some contemporary literature), the CG-induced mechanisms for producing pulmonary edema were thought to be the liberation of HCl in the lung and subsequent damage to the epithelial and endothelial surfaces.[176] This HCl theory has now been integrated to a broader explanation, and the hypothesis that most authorities accept is that individuals exposed to high concentrations or high doses of CG suffer damage caused by at least two separate chemical reactions: hydrolysis and acylation.[177] Hydrolysis accounts for the early-onset symptoms by irritating mucous surfaces but not for pulmonary edema. Acylation accounts for damage to the lungs and causes the changes that lead to

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171 Ibid., 94.

172 Diller, "Pathogenesis of Phosgene Poisoning," 10.

173 Werner F. Diller, Joachim Bruch, and Walter Dehnen, "Pulmonary Changes in the Rat Following Low Phosgene Exposure," *Archives of Toxicology* 57, no. 3 (1985): 184–190.

174 Vedder, "The Pulmonary Irritants," 89.

175 U.S. Environmental Protection Agency (EPA), *Toxicological Review of Phosgene* (CAS No. 75-44-5) *in Support of Summary Information on the Integrated Risk Information System* (IRIS) (Washington, DC: EPA, December 2005), 5; Belinda Bray, *Poisons Information Monograph 419: Phosgene* (Geneva: International Program on Chemical Safety, WHO, 1997), 10.

176 Robert L. Maynard, "Phosgene," in *Chemical Warfare Agents: Toxicology and Treatment*, 2nd ed., ed. Timothy C. Marrs, Robert L. Maynard, and Frederick R. Sidell (Chichester, England: John Wiley & Sons, Inc., 2007), 479.

177 U.S. Environmental Protection Agency (EPA), *Toxicological Review of Phosgene*, 5; Bray, Poisons Information Monograph, 10; National Research Council, *Fasciculus on Chemical Warfare Medicine. Volume II – Respiratory Tract* (Washington, D.C.: National Academy of Sciences, 1945).

pulmonary edema. The CG hydrolysis reaction is a concentration-based effect while CG acylation reaction is a dosage-based effect.

16. Hydrolysis

CG is only slightly soluble in water, and as a result, CG exposure does not produce large amounts of HCl. Small amounts of HCl do form, however, via hydrolysis of CG in the body. This small amount of HCl appears to trigger early-onset, reflex symptoms when it contacts mucous membranes of the eye, nose, and respiratory tract. This triggering effect is a function of concentration, not of dosage. Not all victims experience these symptoms. For those who do, the symptoms may disappear after exposure ends in as little as 5 minutes, but can last for hours, after which victims return to being asymptomatic.

17. Acylation

For CG exposure, acylation is thought to be the major mechanism for damage to the lungs. Acylation results from the reaction of the CG carbonyl group with nucleophilic moieties, such as the amino, hydroxyl, and sulfhydryl groups of tissue macromolecules. This reaction causes "destruction of proteins and lipoids, irreversible alterations of membrane structure, and disruption of enzyme and other cell functions,"[178] which lead to pulmonary edema.

While the symptom progression for pulmonary edema induced by CG is similar to that of pulmonary edema induced by other causes (e.g., the pulmonary edema that commonly is associated with congestive heart failure), the "pathophysiological mechanisms leading to pulmonary edema from phosgene exposure differ from those leading to cardiogenic pulmonary edema."[179] As recently as 2007, one expert prefaced his extensive discussion of the evolution of pulmonary edema following CG exposure by cautioning that the "exact mechanisms involved remain remarkably obscure."[180]

18. Summary

A person exposed to CG can likely detect the odor and might experience very slight irritation to the eyes and throat, with no signs of lung irritation and with no awareness of the ongoing damage to the lung. The human odor threshold for CG is low, 1.5 to 6 mg/m^3,[181] and at these low concentrations, CG's odor is similar to that of newly mown hay or freshly cut grass or corn. If a soldier fails to adhere to his training to mask upon smelling newly mown hay or if the odor of CG is masked by other odors, he may inhale CG for extended periods at concentrations insufficient to cause immediate symptoms.

178 Borak and Diller, "Phosgene Exposure," 111.
179 Ibid., 116.
180 Maynard, "Phosgene," 484.
181 Sciuto, "Inhalation Toxicology of an Irritant Gas," 472.

Thus, he may not be aware of the lung damage underway until overt pulmonary edema (with its characteristic symptoms) is triggered.

Acute exposure to CG causes victims to potentially experience three distinct temporal phases.[182] The initial phase involves the mild, early-onset symptoms caused by the production of HCl: irritation to the eyes, throat, and upper respiratory pathway; shallow respiration; and decreased respiratory rate. If the victim ends exposure by moving to fresh air or putting on protective gear, the early-onset symptoms recede within a matter of minutes to hours.

At this point, the victim might have no further symptoms (if the dosage was sufficiently low) or might enter a latent phase before the eventual onset of pulmonary edema (if the dosage was sufficiently high). The length of the latent phase can be as short as 30 minutes or as long as a few days. During the latent phase, lung damage progresses toward pulmonary edema, with the victim *asymptomatic* and unaware of the ongoing damage. Edematous swelling begins in the lungs, and blood plasma increases in the pulmonary interstitium and alveoli. The *MMCC* states that the "duration and concentration [dosage] of the exposure will determine the time to symptom onset"[183] and that "[e]ven minimal physical exertion may shorten the clinical latent period and increase the severity of respiratory symptoms."[184]

Eventually, such victims will enter the third phase: progressive pulmonary edema. The following summarizes the descriptions of symptoms associated with CG-induced pulmonary edema found in the literature: progressive respiratory distress with shortness of breath, which progresses to a sense of suffocation ("dry-land drowning") accompanied by a high state of anxiety; dry coughing, which progresses to constant, painful wet coughing that produces a large amount of frothy sputum; pain in the chest; nausea and vomiting; a burning sensation of the upper airways. This third phase ends with death or recovery, depending on the severity and the availability of medical treatment. As mentioned previously, higher dosage implies faster onset and higher severity of pulmonary edema.

In terms of the *AMedP-7.5* methodology, it is interesting that there appears to be no known "moderate" severity symptom complex caused by CG poisoning. One might presume that the irritation symptoms could worsen to the point of becoming "moderate"; however, on the basis of clinical experience in WWI, Vedder minimizes the importance of the irritant effects of CG even for high concentration CG, stating that relative to chlorine, "[p]hosgene causes practically no irritation of the trachea and bronchi and subjective

182 Borak and Diller, "Phosgene Exposure," 112; U.S. Environmental Protection Agency (EPA), *Toxicological Review of Phosgene*, 6.

183 Hurst et al., *Medical Management of Chemical Casualties*, 30–31, 35.

184 Ibid., 35.

irritation is much less in evidence."[185] Thus, concentration-based effects are modeled only as mild (Severity Level 1) irritation.

The dosage-based effects are described in the literature purely in terms of the initial *asymptomatic* lung damage and eventual pulmonary edema, which is either Severe or Very Severe on the *AMedP-7.5* scale—never Mild or Moderate. Intuitively, and from the phrase "progressive" respiratory distress, it seems that a person might experience a brief period of Mild or Moderate symptoms as pulmonary edema begins to cause symptoms, but most literature descriptions do not provide any detail on such a period. Again, Vedder's clinical experience is instructive: he notes that a person "may feel able to carry on his work for an hour or two with only trivial symptoms, but then becomes suddenly rapidly worse."[186] Thus, whatever short period of Mild or Moderate symptoms a person may experience is ignored for the models. This will make no practical difference on the casualty estimates produced by *AMedP-7.5*.

Table 68 and Table 69 summarize the previous qualitative descriptions of the physiological effects after inhalation of CG.

Table 68. Association of CG Injury Severity Levels with Dosage-Dependent CG Symptom Sets

Injury Severity Level	Set of Symptoms
0	No observable injury
3 (severe)	Pulmonary edema (progressive respiratory distress; anxiety; dry and then painful wet cough; chest pain; nausea and vomiting)
4 (very severe)	More severe and rapidly progressing pulmonary edema (progressive respiratory distress; anxiety; dry and then painful wet cough; chest pain; nausea and vomiting; loss of consciousness)

Table 69. Association of CG Injury Severity Levels with Concentration-Dependent CG Symptom Sets

Injury Severity Level	Set of Symptoms
0	No observable injury
1 (mild)	Nausea; transient irritation to the eyes, nose and throat; anxiety; shortness of breath; mild dry cough

185 Vedder, "The Pulmonary Irritants," 94.

186 Ibid.

Toxicity Parameters and Concentration Ranges (*AMedP-7.5 Tables 4-26 and 4-28*)

Since CG's effects can be segregated into dosage-based and concentration-based, the next two Subsections address dosage-based effects and concentration-based effects.

1. Dosage-Based Toxicity Parameters

The CSAC report is FOUO, so it was not used. ECBC-TR-856 reports the LCt_{50} to be 1500 mg-min/m^3 with an associated probit slope of 11 probits/log (dose). It also specifies an $ECt_{50\text{-severe}}$ of 250 mg-min/m^3 with the same probit slope as the lethal level.[187] The description makes clear that these estimates relate to dosage-based pulmonary edema effects. ECBC-TR-856 provides the most trustworthy toxicity estimates among sources that could be used in a NATO document without a "NATO UNCLASSIFIED" or higher marking.[188]

The estimated $ECt_{50\text{-severe}}$ of 250 mg-min/m^3 reported in ECBC-TR-856 is derived from the LCt_{50} estimate of 1500 mg-min/m^3 by applying the ratio of AEGL ECt_{50}/AEGL LCt_{50} (a ratio of 1/6). This estimated median toxicity can be compared with the available literature data,[189] which suggests that at dosages of >30 ppm-min (123 mg-min/m^3) initial lung damage occurs and at dosages of >150 ppm-min (617 mg-min/m^3) delayed pulmonary edema will occur. As noted in ECBC-TR-856, these two dosages "roughly encompass the range of effects that could be considered severe effects and thus could serve as the lower and upper limits of the estimated $ECt_{50\text{-severe}}$."[190] Accordingly, if the $ECt_{01\text{-severe}}$ is set to 123 mg-min/m^3, then the corresponding $ECt_{50\text{-severe}}$ would equal 215 mg-min/m^3, and if the $ECt_{99\text{-severe}}$ is set to 615 mg-min/m^3, then the corresponding $ECt_{50\text{-severe}}$ would be 350 mg-min/m^3 (if the probit slope is 11 probits/log (dose)). The median of the two calculated corresponding values (215 mg-min/m^3 and 350 mg-min/m^3) is 283 mg-min/m^3, which is close to the proposed estimated $ECt_{50\text{-severe}}$ of 250 mg-min/m^3 and an estimate that is consistent with the available data. However, this estimate should be revisited if better supporting data become available.

ECBC-TR-856 does not give values for moderate or mild effects, consistent with the previous observation that there is apparently no dosage-based effect from CG other than delayed pulmonary edema. All other observed effects (e.g., instantaneous local irritation)

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187 Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*, 27.

188 See the following report for information on alternate toxicity estimate sources: Oxford et al., *Parameters for Estimation of Casualties*, 34.

189 Borak and Diller, "Phosgene Exposure"; Werner F. Diller and R. Zante, "Dosis-Wirkungs-Beziehungen bei Phosgen-Einwirkung auf Mensch und Tier," *Arbeitsmedizin* 32 (1982): 360–368; Sciuto, "Inhalation Toxicology of an Irritant Gas," 473. Borak and Diller state a range of 25–50 ppm-min for initial lung damage, Diller and Zante state "> than 30 ppm-min" for the same effect, and Sciuto lists greater than 30 ppm-min for the same effect.

190 Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*, O-3.

are concentration based and are discussed in the next section. To be thorough, we searched for any additional data that could indicate the existence of mild or moderate effects in humans or animals. We found no such data for humans. Although many studies of CG inhalation in animal models are available, most focus on lethality testing. The AEGL document for CG[191] and the Environmental Protection Agency's (EPA) toxicological review of CG[192] appear to summarize the entirety of the sublethal inhalation animal data. Many of the studies cited relate to low-level chronic exposure to determine long-term tolerance. These studies are not relevant for *AMedP-7.5*. Table 70 summarizes the few studies that used exposure scenarios that could be considered relevant for *AMedP-7.5*.

Examination of the reported signs and symptoms shows that in most cases,[193] only subclinical effects were observed. To state it differently, although laboratory study could identify that CG had caused some negative effect, no clear symptoms were evident.[194] These sources do not provide relevant information for defining a moderate or mild ECt_{50}, since an ECt_{50} would be associated with some definite symptoms.

Pauluhn, however, described two experiments in which some animals had what might be called moderate symptoms on the *AMedP-7.5* severity scale. Pauluhn measured the changes in various bronchoalveolar lavage fluid (BAL) markers (protein, soluble collagen, polymorphonuclear leukocytes (PMN) counts, and alveolar macrophages) for 3 months after exposing rats to CG at various concentrations for 30 and 240 minutes.[195] The clinical signs observed include irregular and labored breathing patterns, tachypnea, and loss of body weights for rats exposed to 190 mg-min/m^3 or greater. BAL fluid protein was among the most sensitive endpoints to probe the CG-induced pulmonary effects. He observed that doses of ~200 mg-min/m^3 or greater cause a distinctive and significant increase in BAL fluid protein at Day 1 post-challenge, which suggested pulmonary damage. Pulmonary edema was observed in 50% of the animals exposed to 1008 mg-min/m^3.

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191 National Research Council, "Phosgene."

192 U.S. Environmental Protection Agency (EPA), *Toxicological Review of Phosgene* (Washington, D.C.: EPA, December 2005).

193 William E. Rinehart and Theodore Hatch, "Concentration-Time Product (Ct) as an Expression of Dose in Sublethal Exposures to Phosgene," *American Industrial Hygiene Association Journal* 25, no. 6 (1962): 545–553; Diller, Bruch, and Dehnen, "Pulmonary Changes in the Rat"; William D. Currie, Gary E. Hatch, and Michael F. Frosolono, "Pulmonary Alterations in Rats Due to Acute Phosgene Inhalation," *Fundamental and Applied Toxicology* 8, no. 1 (1987): 107–114; William D. Currie, Gary E. Hatch, and Michael F. Frosolono, "Changes in Lung ATP Concentration in the Rat after Low-Level Phosgene Exposure," *Journal of Biochemical Toxicology* 2 (Summer 1987): 105–114.

194 Admittedly, it may be difficult to observe symptoms in rats, which is really an argument against using rats as surrogates for humans.

195 Jürgen Pauluhn, "Acute Nose-Only Exposure of Rats to Phosgene. Part II. Concentration × Time Dependence of Changes in Bronchoalveolar Lavage During a Follow-up Period of 3 Months," *Inhalation Toxicology* 18, no. 9 (2006a): 595–607.

Table 70. Summary of Relevant Non-Lethal Animal Inhalation Exposures to CG

Source	Animal	Physiological or Biochemical Metric	Signs and Symptoms	Threshold Ct Causing Effect (mg-min/m^3)
Rinehart and Hatch	Rat	Pulmonary gas exchange	Pulmonary damage	123
Diller, Bruch, and Dehnen	Rat	Bronchoalveolar lavage fluid (BAL) fluid protein; histopathology	Pulmonary damage	206
	Rat	Histopathology	Widening of pulmonary interstices	103
Currie, Hatch, and Frosnolo	Rat	Body weight/lung weight	Pulmonary edema	493
	Rat	BAL fluid protein	Pulmonary damage	246
	Rat	BAL fluid protein	Pulmonary damage	197
Pauluhn, 2006a	Rat	BAL fluid protein	Irregular and labored breathing patterns, tachypnea, and loss of body weights; pulmonary damage	200
Pauluhn, 2006b	Dog	BAL fluid protein	Transient and minor nasal discharge, salivation, and lacrimation suggesting mucosal irritation; pulmonary inflammation	495
—	Dog	BAL fluid protein	Distinct irregular and labored breathing patterns, reddened conjunctivae, reddened mucosae of the oral cavity, and vomitus with rales; pulmonary edema	1050

Note: See Appendix B for full reference citations.

Another paper by Pauluhn[196] reports on exposure of dogs to sublethal doses (270, 495, and 1050 mg-min/m^3) of CG. He examined the BAL markers, lung weights (increased weight can indicate pulmonary edema), and lung histopathology at 24 hours post-challenge. The study revealed that borderline changes to BAL markers were observed at 495 mg-min/m^3 while increases in lung weights and BAL markers were observed at 1050 mg-min/m^3. Histopathological examinations showed a mild, but distinctive, inflammatory response at the bronchoalveolar level at 495 mg-min/m^3, but a more severe response with

196 Jürgen Pauluhn, "Acute Head-Only Exposure of Dogs to Phosgene. Part III. Comparison of Indicators of Lung Injury in Dogs and Rats," *Inhalation Toxicology* 18, no. 9 (2006b): 609–621.

serofibrinous exudates and edema was detected at 1050 mg-min/m^3. Dogs exposed to the two lower doses showed transient and minor nasal discharge, salivation, and lacrimation, which suggested mucosal irritation. At the highest dose, the animals exhibited "distinct irregular and labored breathing patterns, reddened conjunctivae, reddened mucosae of the oral cavity, and vomitous (colorless foam) with rales (auscultation) on the first postexposure day."[197]

The dogs that received the higher dose clearly had Severe symptoms, so the Ct of 1050 mg-min/m^3 cannot be used to estimate toxicity parameters for mild or moderate effects. However, Pauluhn's rats that inhaled 200 mg-min/m^3 and dogs that inhaled 495 mg-min/m^3 appear to have had mild or moderate symptoms. If such data are to be used to estimate human toxicity parameters, these data must be scaled according to minute volumes and body mass. This process will result in higher values, so it is immediately obvious that the dog data conflict with the $ECt_{50\text{-severe}}$ from ECBC-TR-856. Even before scaling to humans, the moderate value for dogs is higher than the severe value for humans. Similarly, scaling the rat value to human minute volume and mass[198] yields a value of 317 mg-min/m^3, which is also greater than the human ECt_{50} from ECBC-TR-856.

These inconsistencies are likely an issue of cross-species differences. Cross-species differences may also be the reason that there appears to be a mild or moderate endpoint in rats,[199] but no evidence of such an endpoint in humans (as discussed in Section 0). Thus, the final set of toxicity parameters includes only Severe and Very Severe values, as summarized in Table 71. The parameter values are from ECBC-TR-856.

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[197] Ibid., 612.

[198] Using values reported by R. W. Bide, S. J. Armour, and E. Yee, "Allometric Respiration/Body Mass Data for Animals to Be Used for Estimates of Inhalation Toxicity to Young Adult Humans," *Journal of Applied Toxicology* 20, no. 4 (2000): 273–290.

[199] Since the dogs were sacrificed for histopathological examination at 24 hours, it is not clear that the symptoms described were truly an endpoint. The symptoms might have worsened if the dogs were alive.

Table 71. Median Toxicities and Probit Slopes for Inhaled CG

Injury Profile	Effect	Median Toxicity[a] (mg-min/m^3)	Probit Slope (Probits/Log (dose))
CG Very Severe	Lethal	1500	11.0
CG Severe	Severe	250	11.0

[a] The median toxicity is an estimate for a 2-minute exposure.

2. Concentration Thresholds

The literature[200] commonly notes that symptoms of mild eye and throat irritation, mild coughing, shortness of breath, and mild nausea, occur after exposures to a concentration of >12 mg/m^3 (>3 ppm) (see Table 72). But not everyone experiences these symptoms. For those who do, presumably, these symptoms might worsen, or a person might become more likely to experience each symptom as the concentration increases. Since no data are available to indicate how to model this progression, the irritation symptoms are not broken into multiple ranges. Although we were unable to trace to original data the statements of 3 ppm being the threshold, we also did not find any evidence to the contrary. Thus, there is a single concentration threshold, above which mild (Severity Level 1) symptoms are estimated to occur.

Table 72. CG Concentration Ranges

Injury Profile[a]	Concentration Range (mg/m^3)
(none)	<12
[CG] Mild	≥12

[a] The symbol [CG] is used to refer to CG concentration-based effects, to distinguish these Injury Profiles from those in Table 71. These effects are from both inhalation and ocular exposure.

Injury Profiles (*AMedP-7.5 Tables 4-27 and 4-29*)

This section draws upon the USAMRICD Handbooks[201] and selected case reports to develop CG Injury Profiles and reports that summarize clinical experience with CG casualties from WWI. Many other case reports exist, but, as noted by the EPA in its review of phosgene,[202] much of the data are anecdotal or lack specificity in terms of the progression of injury over time. In addition, many reports discuss chronic illness from day-to-day exposure to small quantities of CG, which is not useful for the present purpose. The specific case reports used in this analysis were selected because they involved short-term

200 Sciuto, "Inhalation Toxicology of an Irritant Gas," 472; U.S. Environmental Protection Agency (EPA), *Toxicological Review of Phosgene*, 38; National Research Council, "Phosgene," Table 1–5; Diller, "Pathogenesis of Phosgene Poisoning," 8–9.

201 Hurst et al., *Medical Management of Chemical Casualties*; Hurst et al., *Field Management of Chemical Casualties.*

202 U.S. Environmental Protection Agency (EPA), *Toxicological Review of Phosgene*, 6.

events (e.g., pipes bursting) that would produce conditions similar to those of a soldier encountering CG in a combat zone and contained enough information on the timing of symptoms. The WWI clinical experience summaries were used, despite being somewhat vague, because they are clearly based on actual chemical warfare casualties.

The discussion focuses on the three temporal phases of CG poisoning: early-onset irritation, asymptomatic latency, and pulmonary edema. Early-onset irritation is relevant for the [CG] Mild Injury Profile, and asymptomatic latency and pulmonary edema are relevant for the CG Severe and Very Severe Injury Profiles

For the concentration-based mild effects, it is widely stated that that the symptoms appear immediately. Thus, the Injury Profile begins at Injury Severity Level 1 at time zero. Borak and Diller[203] state that the initial irritation phase may last for hours, while some case reports describe the initial symptoms receding in 5[204] to 20 minutes[205] for healthy, young males. Borak and Diller are likely describing the general population, so the data for healthy, young males are more relevant. Based on the assumption that symptoms cease at 15 minutes, the [CG] Mild Injury Profile goes to Injury Severity Level 0 at 15 minutes.[206]

For the Severe and Very Severe Injury Profiles, the initial phase is asymptomatic latency. The USAMRICD Handbooks state that the length of the latent phase is typically between 20 minutes and 24 hours, although it can extend as long as 72 hours.[207] The length of the latent period is "roughly"[208] correlated with the degree of exposure, which makes sense for an agent that chemically reacts with the body (the reaction will only occur to the extent that the agent is present). However, insufficient data are available to develop a quantitative relationship between Ct and duration of latent period. Therefore, for the present model, the best that might be done seems to be to assign different latent periods to the Severe and Very Severe Injury Profiles.

A factor that was once thought to affect the duration of the latent period was physical activity after exposure. The thought was that physical activity would increase the minute volume, and that increase would somehow accelerate the inflammatory cascade (leading

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203 Borak and Diller, "Phosgene Exposure," 112.

204 E. Dale Everett and Edwin L. Overholt, "Phosgene Poisoning," *Journal of the American Medical Association* 205, no. 4 (1968): 243–245.

205 S. Delephine, "Summary Notes on Two Fatalities Due to Inhaling Phosgene," *Journal of Industrial Hygiene* 4 (1922): 433–440. As cited by National Research Council, "Phosgene," 22.

206 Table 74 shows the complete CG Injury Profiles.

207 Hurst et al., *Medical Management of Chemical Casualties*, 30; Hurst et al., *Field Management of Chemical Casualties*, 60.

208 H. D. Bruner and Dale R. Coman, "The Pathologic Anatomy of Phosgene Poisoning in Relation to the Pathologic Physiology," in *Fasciculus on Chemical Warfare Medicine. Volume II – Respiratory Tract*, ed. National Research Council, Committee on Treatment of Gas Casualties (Washington, D.C.: National Academy of Sciences, 1945), 269.

to pulmonary edema) and exacerbate the damage, thus shortening the latent period and worsening the prognosis. Evidence from animal studies shows that physical activity after exposure is not a very critical factor, however.[209] That said, rest is still part of the recommended treatment for CG casualties (for several reasons).

The civilian victims of accidental CG poisoning discussed in the case reports had latent periods varying from 4 to 12 hours (see Table 73). In Table 73, no apparent correlation seems to exist between the length of latency period and the outcome. The variation of the latent period appears to be more dependent on the individual (random). However, the USAMRICD Handbooks indicate that 6 hours is a threshold latent period: casualties who present with symptoms leading to pulmonary edema between 2 and 6 hours after exposure may die even if medical treatment is provided, and casualties who present later than 6 hours after exposure will likely survive if medical treatment is provided.[210] These statements are not linked to specific data, and the Table 73 data seem to indicate no correlation. But Table 73 is a small dataset, and the USAMRICD Handbooks contain the distilled knowledge from some of the foremost modern medical experts on these topics, so it seems reasonable to take their statements at face value.

Based on the USAMRICD Handbooks, we assigned a latent period of 4 hours (the average of 2 and 6 hours) to the Very Severe Injury Profile. Based on the longest latent periods in the case reports (see Table 73), we assigned a latent period of 12 hours to the Severe Injury Profile. Although it has been reported that the latent period can last as long as 72 hours, Vedder states that "pulmonary edema reaches its height in about twenty-four hours" and the USAMRICD Handbooks state that "most significant exposures have a latent period of less than 24 hours."[211] Since the reporting time resolution of *AMedP-7.5* is 1 day, the difference between 4, 12, and even 24 hours is negligible. Thus, although the assigned latent periods are somewhat arbitrary and there is a known variance in actual patients, the model should be sufficiently accurate for *AMedP-7.5*.

The next phase of the injury progression is pulmonary edema. While it is clear that the onset of pulmonary edema occurs over time, no sources give quantifiable estimates of the timing of the onset of various symptoms. Vedder, however, gives the impression of a very rapid progression, by stating that patients at field hospitals during WWI who were

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209 Smith Freeman, F. S. Grodins, and A. J. Kosman, "The Effects of Exercise after Exposure to Phosgene," in *Fasciculus on Chemical Warfare Medicine. Volume II – Respiratory Tract*, ed. National Research Council, Committee on Treatment of Gas Casualties (Washington, D.C.: National Academy of Sciences, 1945), 582–589. Likely, exercise makes the *immediate* symptoms (shortness of breath) worse because the person cannot receive adequate oxygen.

210 Hurst et al., *Medical Management of Chemical Casualties*, 31–32; Hurst et al., *Field Management of Chemical Casualties*, 60–63.

211 Hurst et al., *Field Management of Chemical Casualties*, 60; Hurst et al., *Medical Management of Chemical Casualties*, 30.

showing no symptoms upon getting out of bed to go to the latrine would have symptoms requiring immediate medical care upon their return.[212] Thus, although it is somewhat counterintuitive, it seems reasonable to define a sudden change from Injury Severity Level 0 to the maximum severity (3 or 4) for each Injury Profile at the end of the latent period.

Table 73. Summary of Case Reports on CG-Induced Pulmonary Edema

Source	Number of People	Length of Latent Period (Hours)	Received Medical Treatment? (Y/N?)	Time Until Death (Hours)	Time Until Discharge (Days)
Vedder	1	4.5	Y	6	N/A
Ireland	1	4–5	Y	6	N/A
Lim et al.	1	10	Y	Estimated as 13	N/A
———	5	6–12	Y	N/A	5 to 14
Nisra, Manoria, and Saxena	1	7.5	Y	18	N/A
Regan	1	8	Y	N/A	6
———	1	11	Y	N/A	12
Stavrakis	1	6–12	Y	12.5	
———	1	4	Y	N/A	5
Everett and Overholt	1	6	Y	N/A	5
Delephine	2	4	N	N/A	>1 day

Note: See Appendix B for full reference citations.

Since the Injury Profiles reflect the case with no medical treatment, the Severe and Very Severe Injury Profiles will end in death, which is consistent with statements by the USAMRICD Handbooks that casualties with longer latent periods are likely to survive *if prompt medical treatment is provided*.[213] Thus, the remaining information needed to complete the Injury Profiles is the time until death. On that point, the USAMRICD Handbooks do not provide any information. Vedder, writing about experience with casualties who *did* receive medical treatment, states that "four-fifths of the deaths occur in the first twenty-four hours [and v]ery few die after the third day."[214] Thus, both Injury Profiles—which are intended to represent the median individual—should indicate death within 1 day. Since the time resolution of *AMedP-7.5* is 1 day, "within 1 day" is the most important point. The case report data can also be used to estimate more specific times, but

212 Vedder, "The Pulmonary Irritants," 89.

213 Hurst et al., *Field Management of Chemical Casualties*, 61; Hurst et al., *Medical Management of Chemical Casualties*, 32.

214 Vedder, "The Pulmonary Irritants," 90.

it must be acknowledged that these more specific estimates are based on a very small dataset.

If the case reports are to be used, they must first somehow be assigned to an Injury Profile, which can be done based on the length of the latent periods. Two cases in Table 73 had a latent period less than 6 hours, and a fatal outcome occurred 6 hours after exposure.[215] As the only specific estimates available, these estimates are used to set the time to death for the Very Severe Injury Profile at 6 hours, or 360 minutes. Three cases had latent periods longer than 6 hours, and the average time until death—and therefore the estimated time to death for the Severe Injury Profile—is 14.5 hours, or 870 minutes.

Table 74 and Table 75 summarize the CG Injury Profiles.

Table 74. Inhaled CG Injury Profiles

Time Point (min)	CG Severe	CG Very Severe
1	0	0
240	0	3
360	0	4[a]
720	3	
870	4[a]	

[a] Death is modeled to occur at this point.

Table 75. Peak CG Concentration Injury Profile

Time Point (min)	[CG] Mild
1	1
15	0

Medical Treatment (*AMedP-7.5 Table 4-30*)

3. Efficacy of Medical Treatment

No antidote is available for CG poisoning.[216] The physiological mechanisms leading to pulmonary edema from CG poisoning are different from those leading to cardiogenic pulmonary edema. As a result, "many drugs and interventions that have proved to be useful for treating other forms of pulmonary edema have failed in CG-exposure victims."[217] Pulmonary emergency treatment has saved a number of victims of CG exposure, and

215 It is clear from the descriptions in each original source that these case reports are not referring the same event despite the similarity in the numbers: one victim was a chemist and the other was a soldier.

216 Agency for Toxic Substances and Disease Registry, *Medical Management Guidelines for Phosgene* (*$COCL_2$*) (Atlanta, GA: ATSDR, 2011), 16.

217 Borak and Diller, "Phosgene Exposure," 116.

although there is no antidote for CG, Borak and Diller note that a "major goal in victim management has been to block the phosgene-induced inflammatory cascade during the latency phase, before the development of clinical edema."[218]

Case reports and the USAMRICD Handbooks do not provide any quantifiable description of the effect of medical treatment. Thus, there is no basis for estimating a protection factor. The USAMRICD Handbooks do indicate that casualties who present with symptoms leading to pulmonary edema between 2 and 6 hours after exposure will likely die even if medical treatment is provided, and casualties who present later than 6 hours after exposure will likely survive if medical treatment is provided.[219] The available records of knowledge based on WWI experience do not provide any contradicting or additional information.[220]

Thus, for the "with treatment" cases, we assumed that 100% of casualties following the Severe Injury Profile would survive and 0% of casualties following the Very Severe Injury Profile would survive. This is a significant simplification of what the USAMRICD Handbooks actually state, but given that there are no true data available, there is no other good option.

4. MTOR Table

Table 76 is the MTOR table for CG casualties. It is derived from the Injury Profiles, human case reports, guidelines from a couple of modern U.S. military sources, and reports based on clinical experience with CG casualties during WWI.

Medical treatment comprises supportive care with forced bed rest. As discussed previously, the only modeled effect is that casualties in the Severe Injury Profile will not die. The *MACW* indicates that sequelae are rare,[221] and the USAMRICD Handbooks do not mention sequelae. Ireland states that of 1,000 CG WWI casualties, only 4 were discharged "for disabilities directly attributed to gas."[222] Thus, the model includes 0% permanent disability (permanent CONV) for all Injury Profiles.

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218 Ibid., 115.

219 Hurst et al., *Medical Management of Chemical Casualties*, 31–32; Hurst et al., *Field Management of Chemical Casualties*, 60–63.

220 Vedder, "The Pulmonary Irritants"; Merritte Weber Ireland, *Medical Aspects of Gas Warfare*, vol. XIV of *The Medical Department of the United States in the World War*, ed. Frank W. Weed. Washington, DC: Government Printing Office, 1926).

221 Tuorinsky and Sciuto, "Toxic Inhalational Injury," 361.

222 Ireland, *Medical Aspects of Gas Warfare*, 284.

In the discussions that follow, which explain Table 76, the potential for administrative declaration of asymptomatic "casualties" or delay of RTD for additional monitoring[223] is ignored. This approach is consistent with the limitation discussed in Section 0.

Based on the Injury Profile, [CG] Mild cohort casualties will recover sufficiently to RTD on Day 1, so they are reported as RTD on Day 2 in the MTOR. The availability of medical treatment has no impact on the modeled outcome for this Injury Profile.

For the CG Severe Injury Profile, we assumed (see Subsection 1.B.3) that medical treatment will prevent casualties from dying. Thus, an estimate of the timing of recovery is needed. The *MMCC* only says that the earliest potential RTD would be 48 hours, but that outcome applies only if several clinical parameters are normal[224]—in other words, it is for someone who initially appeared to have had a serious exposure but in fact did not. The *MACW* does not provide guidance on the timeline of recovery for CG patients. In Table 73, the hospital discharge times are between 5 and 14 days. But as Wyatt and Allister note, "Complete recovery after phosgene exposure may take a long time, and most patients continue to complain of exertional dyspnoea for several months after exposure."[225] However, most important (because it is linked to actual war casualties), Ireland states that an analysis of 1,000 CG casualties from WWI showed that the average period of hospitalization was 44.7 days.[226] Unfortunately, no other statistical information is provided for the 1,000 WWI casualties, and the book cites personnel records that are no longer available.

Since hospital discharge typically does not mean that the person is fully healthy, the Table 73 and previous WWI casualty data can be used to estimate a time to CONV for CG Severe casualties. The only information relevant for RTD is the statement by Wyatt and Allister. Although it is undesirable to estimate time to RTD using such general statements, it is also undesirable to avoid estimating RTD when it is known that most casualties will eventually be able to RTD. Thus, time to RTD is estimated as 3 months (90 days). Although we would prefer to provide some indication of the distribution of times, the literature sources do not provide any supporting data or even vague statements to inform the development of such a distribution.

To represent the approximate range of hospitalization time without making an overly detailed model, time to CONV is given in weekly intervals, based on a triangle distribution with a minimum of Day 7 (approximately the minimum observed in Table 73), a mode of

223 Such as the 24-hour monitoring recommended by Hurst et al., *Medical Management of Chemical Casualties*, 35–38.

224 Hurst et al., *Medical Management of Chemical Casualties*, 39.

225 J. P. Wyatt and C. A. Allister, "Occupational Phosgene Poisoning: A Case Report and Review," *Journal of Accident and Emergency Medicine* 12, no. 3 (1995): 213.

226 Ireland, *Medical Aspects of Gas Warfare*, 283.

44.7 days (based on WWI data), and a maximum of 2 months (loosely based on Wyatt and Allister and being shorter than time to RTD). It is acknowledged that the exact numbers are somewhat arbitrary. This approach was taken because it seems important to represent the *fact* of the distribution in times even though it cannot be done with great accuracy.

For the Very Severe Injury Profile, medical treatment is modeled to provide essentially no benefit to the patient, based loosely on statements in the USAMRICD Handbooks.[227] All casualties DOW; the time to DOW is not affected because the progression of pulmonary edema is too rapid for medical care to have much effect. Thus, time to DOW is as indicated by the Injury Profile: 6 hours, and casualties are reported as DOW on Day 2 in the MTOR.

Table 76. CG Medical Treatment Outcome Reporting

Injury Profile	DOW[a]	CONV[a]	RTD[a]
[CG] Mild	0%	0%	Day 2: 100%
CG Severe	0%	Day 14: 2% Day 21: 7% Day 28: 12% Day 35: 17% Day 42: 22% Day 49: 25% Day 56: 13% Day 60: 2%	Day 90: 100%
CG Very Severe	Day 2: 100%	0%	0%

[a] Reported values indicate the fraction that changes status on a given day; they are not cumulative.

227 Hurst et al., *Medical Management of Chemical Casualties*, 31–32; Hurst et al., *Field Management of Chemical Casualties*, 59–63.

1.9. Cl_2 Model
(*AMedP-7.5 Section 4.2.9*)

Introduction

Chlorine (Cl_2), a pulmonary chemical agent that was used during WWI,[228] is now often referred to as a TIC because of its use in the chemical industry,[229] but we refer to it as a chemical agent. As a pulmonary agent, Cl_2's primary mechanism of injury is damage to the lung.

The objective of this chapter is to describe the human response model for Cl_2 as it has been incorporated into *AMedP-7.5*. The chapter first discusses a scoping assumption. Then it describes the physiological effects of Cl_2, the toxicity parameters used in *AMedP-7.5*, development of Injury Profiles, and the medical treatment model.

Assumption (*AMedP-7.5 Section 4.2.9.2*)

> **Assumption**: Percutaneous exposure to Cl_2 vapour and liquid are negligible.

The percutaneous vapor is assumed negligible because in all the research performed in the development of this model, no sources were found that discussed Cl_2 injury resulting from percutaneous vapor exposure. Further, the liquid resulting from a Cl_2 attack, and thus the percutaneous liquid contribution to dose, may be neglected due to the agent's high volatility (though rapid evaporation may cause frostbite).[230] This assumption may result in an underestimate of the number and severity of casualties.

Physiological Effects (*AMedP-7.5 Table 4-31*)

Chlorine, because of its moderate size and intermediate solubility,[231] causes both central and peripheral damage to the lungs. "Centrally acting chemicals affect the respiratory system from the nasopharynx to the bronchioles," whereas peripherally acting compounds "travel to the smallest segments of the respiratory system, the terminal and respiratory bronchioles, the alveolar ducts, the alveolar sacs, and the alveoli."[232]

The focus of Cl_2's irritant qualities is on the mucous membranes of the eyes, nose, throat, and lungs:

> When chlorine gas comes into contact with the water on the lung tissue, a chemical reaction takes place producing hydrochloric acid, hypochlorous acid, and perchloric acid. Hypochlorous acid further reacts to yield yet more

228 Tuorinsky and Sciuto, "Toxic Inhalational Injury," 342 (Table 10-2).
229 Ibid., 343 (Table 10-3).
230 USACMLS, *Chemical/Biological Agents and Compounds*, III-13.
231 Joseph D. Sexton and David J. Pronchik, "Chlorine Inhalation: The Big Picture," *Clinical Toxicology* 36, nos. 1–2 (1998): 88.
232 Tuorinsky and Sciuto, "Toxic Inhalational Injury," 356.

> hypochlorous acid and oxygen-free radicals. Damage to the lung tissue is caused primarily by the oxygen-free radicals, and secondarily by the hydrochloric acid. When cellular proteins are disrupted, damage occurs. Necrosis and sloughing of the lung tissue produce acute respiratory distress.[233]

The following quotations provide a useful summary of the symptoms, although these symptoms do not exactly match the model described in the rest of this chapter.

> Typically, low exposures produce a rapid-onset ocular irritation with nasal irritation, followed shortly by spasmodic coughing and a rapidly increasing choking sensation. Substernal tightness is noted early. […] Minimal to mild, cyanosis may be evident during exertion, and complaints of exertional dyspnea are prominent. Deep inspiration produces a persistent, hacking cough.[234]

> Moderate chlorine exposures result in an immediate cough and a choking sensation. Severe substernal discomfort and a sense of suffocation develop early. Hoarseness or aphonia is often seen, and stridor may follow. Symptoms and signs of pulmonary edema may appear within 2 to 4 hours; radiological changes typically lag behind the clinical symptoms. There may be retching and vomiting, and the gastric contents often have a distinctive odor of chlorine.[235]

> Intense toxic inhalant exposures may cause pulmonary edema within 30 to 60 minutes. Secretions from both the nasopharynx and tracheobronchial tree are copious, with quantities up to 1 L/h reported. Severe dyspnea is so prominent that the patient may refuse to move. On physical examination, the chest may be hyperinflated. Mediastinal emphysema secondary to peripheral air trapping may dissect the skin and present as subcutaneous emphysema. The sudden death that occurs with massive toxic inhalant exposure is thought to be secondary to laryngeal spasm.[236]

Cl_2's impact is most severe on the respiratory system. At low dosages, it causes ocular and respiratory irritation, mild nausea, headaches, and dizziness. At progressively higher dosages, the respiratory irritation becomes chest pain, shortness of breath, coughing, and delayed but potentially life-threatening pulmonary edema. Other symptoms at higher dosage include vomiting and more severe eye irritation, but no other physiological systems become increasingly severe to the same degree as the respiratory system. Table 77

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233 Sonja J. Meyers, "Chlorine Inhalation in a Pediatric Patient," *Journal of Emergency Nursing* 23, no. 6 (1997): 584.

234 John S. Urbanetti, "Toxic Inhalation Injury," in *Medical Aspects of Chemical and Biological Warfare*, ed. Frederick R. Sidell, Ernest T. Takafuji, and David R. Franz, Textbooks of Military Medicine (Washington, DC: OTSG, 1997), 256.

235 Ibid.

236 Ibid.

summarizes the previous qualitative descriptions in a format amenable to use in *AMedP-7.5* and for the analysis presented in this chapter.

Table 77. Association of Cl_2 Injury Severity Levels with Cl_2 Symptom Sets

Injury Severity Level	Set of Symptoms
0	No observable injury
1 (mild)	Nausea; desire to vomit; mild eye irritation; mild shortness of breath; chest tightness, slight irritation of nose and throat; cough; minor nasal congestion and runny nose; headache and dizziness
2 (moderate)	Vomiting; severe eye irritation; frank shortness of breath; some chest pain; difficulty breathing; more pronounced coughing and irritation of the throat; nasal and respiratory congestion with possible phlegm
3 (severe)	Severe shortness of breath; marked chest pain; rapid and restricted breathing; intense coughing; tracheo-bronchitis; delayed onset of pulmonary edema and/or toxic pneumonitis or bronchio-pneumonia
4 (very severe)	Extreme shortness of breath; decreased breath sounds; production of large amounts of frothy liquid; rapid onset of pulmonary edema; coma; death

Toxicity Parameters (*AMedP-7.5 Table 4-31*)

We believe that the toxicity parameter estimates from CSAC are the best available, and since the CSAC Cl report is *not* FOUO, we used its estimates where possible (see Subsection 1.B.8). CSAC estimated the LCt_{50} to be 13,500 mg-min/m^3 for a 2-minute exposure in the healthy population.[237] Since CSAC did not report on the $ECt_{50\text{-severe}}$ value, we used the $ECt_{50\text{-severe}}$ value of 1300 mg-min/m^3 reported in ECBC-TR-856 for a 2-minute exposure in the healthy population.[238]

CSAC, in its original publication on Cl_2 toxicity estimates, estimated that the probit slope for lethal effects was 8.0. CSAC later identified some improvements to the method of estimating probit slopes and, after further analysis of their results for seven chemicals, noted that this estimate could be revised: "based on the subsequent reanalysis of the total database …, a strong argument exists for revising the military probit slope upward from 8 to 10.5 for chlorine."[239] Although CSAC did not officially revise its estimate, the methodology leading to the revised estimate is more consistent with CSAC estimates for other chemicals, so we use it instead of the original CSAC estimate.

Since the mechanism of Cl_2 toxicity does not vary by severity of injury, we assumed that the mild, moderate, and severe probit slopes are equal to the lethal probit slope.[240] This

237 Sommerville et al., *Review and Assessment of Chlorine*, 8–3.

238 Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*, 26.

239 Sommerville et al., *Review and Assessment of Cyanogen Chloride*, B–11.

240 This principle is applied for several agents in Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*.

assumption also helps avoid illogical results, such as two toxicity curves intersecting. For all levels of effect, we use 10.5 as the estimated probit slope.

Our literature review identified several reports on the low-level toxicity study of Cl_2 in humans that can be used for estimating mild and moderate toxicity parameters for this paper. Table 78 lists the human data that we considered to be usable for this purpose.

Table 78. Relevant Non-Lethal Human Inhalational Exposures to Cl_2

Source	Inhaled Ct (mg-min/m^3)	Exposure Duration (min)	Symptoms	Apparent Injury Severity Level
Anglen	348	240	None	0
	696, 1391	240	Itching or burning nose, eyes and throat; tears; cough; runny nose; headache	1
D'Alessandro et al.	174	60	None	0
Joosting and Verbek	174, 348	120	None	0
	696, 1391	120	Eye, nose, and throat irritation; cough	1
Rotman et al.	348	240	None	0
	696	480	None	0
	696	240	Itchy eyes, runny nose, mild burning in the throat	1
	1391	480		1
Shroff, Khade, and Srinivasan	191	1	Immediate dyspnea and coughing; irritation of throat and eyes; headache; giddiness; chest pain; and abdominal discomfort	2

Note: See Appendix B for full reference citations.

Since Cl_2 has a toxic load exponent greater than 1 (n = 2.75),[241] we deemed it necessary to use EPD calculations in an attempt to compensate for the data only being from exposures over a long time. Calculating dosages without accounting for toxic load effects yields meaningless dose values when compared to the lethal and severe toxicity estimates.

Using the EPD formula given in Subsection 0, we calculated the estimated human EPD (see Table 79). Table 79 shows the following: in five cases in which the EPD is less than 26 mg-min/m^3, the apparent Injury Severity Level was 0; in six cases in which the EPD is between 33 and 103 mg-min/m^3, the apparent Injury Severity Level was 1 (mild);

241 Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*, 26. This value is derived for lethal effects and then applied to other levels of effect.

and in one case in which the EPD was 191 mg-min/m^3, the apparently Injury Severity Level was 2 (moderate).

Table 79. Estimated Human EPDs from Table 78 Data

Source	EPD-Adjusted Dose (mg-min/m^3)	Apparent Injury Severity Level
Anglen	17	0
———	33, 66	1
D'Alessandro et al.	20	0
Joosting and Verbek	13, 26	0
———	51, 103	1
Rotman et al.	17, 21	0
———	33, 43	1
Shroff, Khade, and Srinivasan	191	2

Note: See Appendix B for full reference citations.

Several options are available for using the six EPDs that led to mild symptoms to estimate an $ECt_{50\text{-mild}}$. Seemingly reasonable options include the average of the values, the median of the values, and the average of the highest and lowest values. Since no metric is available for determining which strategy is best, we arbitrarily chose the latter, which gives an estimated $ECt_{50\text{-mild}}$ of 70 mg-min/m^3 (rounded from 68 mg-min/m^3).

Only one report—Shroff, Khade, and Srinivasan—related to moderate symptoms. A chemical company manufacturing caustic chemicals in Bombay experienced an accidental Cl_2 gas leak from a storage tank that caused 88 people to be admitted to the hospital within an hour of exposure to the Cl_2. The level of Cl_2 in the atmosphere at the time was measured to be 66 ppm (191 mg-min/m^3), and all exposed individuals experienced immediate symptoms upon exposure: "All patients presented with immediate dyspnea and coughing. Other symptoms included irritation of the throat and eyes, headache, giddiness, chest pain and abdominal discomfort."[242] Sommerville and Channel labeled the effects "moderate,"[243] (we agree with their assessment) and estimated the exposure time to be as short as 1 minute. Since some patients were surely exposed for longer than 1 minute, the estimated *minimum* Ct that caused moderate effects in the 88 people exposure during the incident was 191 mg-min/m^3.

242 Chandralekha P. Shroff, Megha V. Khade, and Mahalaxmi Srinivasan, "Respiratory Cytopathology in Chlorine Gas Toxicity: A Study in 28 Subjects," *Diagnostic Cytopathology* 4, no. 1 (1988): 28.

243 Douglas R. Sommerville and Stephen R. Channel, *Proposed Provisional Human Toxicity Estimates for Military Operations—Chlorine* (APG, MD: ECBC, 20 August 2009), Table 4.

Since only a single human data point was available to estimate the moderate effects in humans after Cl_2 exposure, we considered animal data. In reviewing the literature, we found that most of the animal studies focused on determining the lethal dosage of Cl_2, with little information given on the symptoms experienced by the test animals. Such data proved useful to Sommerville, Channel, and Bray[244] in developing their estimate of the LCt_{50} (but are not useful for for estimating $ECt_{50\text{-moderate}}$). There were also a few reports on sublethal inhalation animal experiments. The 2004 AEGL report for Cl_2 provides a set of sublethal inhalational data from laboratory animals.[245] Most of the data are from rodent models, but a few are from rabbit, guinea pig, or NHP models. Unfortunately, most of the reports cannot be used for estimating $ECt_{50\text{-moderate}}$ because the purpose of the studies was to determine the long-term tolerance levels. For example, one study was performed for 2 years. This leaves only two rodent studies—a rat model and a mouse model—that might help derive the $ECt_{50\text{-moderate}}$ estimate.[246]

Other studies have demonstrated that a variety of chemical irritants causes a decrease in respiratory rate in different species (cats, dogs, mice, rats, rabbits, guinea pigs, and man).[247] Thus, any attempt to convert an animal Ct to a human Ct requires the measurement of the animals' minute volume before and after (and better, during) the exposure. Using a generic value for the "standard" rat or mouse[248] will not suffice. Since neither the Sommerville, Channel, and Bray report nor the AEGL report provide measured minute volume, the data cannot be extrapolated to a human estimate with meaningful results.[249]

This situation leaves us with the single report on human data—Shroff, Khade, and Srinivasan. This report did not note specifically when the concentration of Cl_2 was measured, but it seems reasonable to assume that it was around the time of the accident. As described previously, 191 mg-min/m^3 is the estimated *minimum* Ct to cause moderate

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244 Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*, Appendix B.

245 National Research Council, "Chlorine: Acute Exposure Guideline Levels," vol. 4 of *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (Washington, DC: National Academies Press, 2004), 37.

246 R. Demnati et al., "Histopathological Effects of Acute Exposure to Chlorine Gas on Sprague-Dawley Rat Lungs," *Journal of Environmental Pathology, Toxicology, and Oncology* 14, no. 1 (1995): 15–19; Craig S. Barrow et al., "Comparison of the Sensory Irritation Response in Mice to Chlorine and Hydrogen Chloride," *Archives of Environmental Health* 32, no. 2 (1977): 68–76.

247 Yves Alarie, "Sensory Irritation of the Upper Airways by Airborne Chemicals," *Toxicology and Applied Pharmacology* 24, no. 2 (1973): 279–297; Yves Alarie, "Bioassay for Evaluating the Potency of Airborne Sensory Irritants and Predicting Acceptable Levels of Exposure in Man," *Food and Cosmetics Toxicology* 19, no. 5 (1981): 623–626.

248 Such values are available from Bide, Armour, and Yee, "Allometric Respiration/Body Mass Data."

249 We tried various strategies of using the data and never arrived at useful results (analysis not shown).

effects. Since there are a number of variables—the movement of individuals out of the toxic area, the change in the level of chlorine gas in the atmosphere over time, and the actual exposure duration experienced by each individual—about which we have no information, we can only use the 191 mg-min/m^3 value. To use the value, it must be set equal to $ECt_{xx\text{-moderate}}$, where xx is some small number to represent that 191 mg-min/m^3 is at the lower end of the toxicity curve. We arbitrarily chose xx = 01, which results in an estimated $ECt_{50\text{-moderate}}$ of 317 mg-min/m^3. This value is rounded to 300 mg-min/m^3, given the high uncertainty.

Table 80 summarizes the set of median toxicities and probit slopes for inhaled Cl_2.

Table 80. Median Toxicities and Probit Slopes for Inhaled Cl_2

Injury Profile	Effect	Median Toxicity[a] (mg-min/m^3)	Probit Slope (Probits/Log (dose))
Cl_2 Very Severe	Lethal	13500	10.5
Cl_2 Severe	Severe	1300	10.5
Cl_2 Moderate	Moderate	300	10.5
Cl_2 Mild	Mild	70	10.5

[a] The median toxicity is an estimate for a 2-minute exposure.

Injury Profiles (*AMedP-7.5 Table 4-32*)

The extent of injury after Cl_2 exposure depends on the concentration, duration of the exposure, and the water content of the tissue exposed.[250] Different physiological systems of the human body are adversely affected by Cl_2 including the respiratory, ocular, gastrointestinal (GI), cutaneous, and neurological systems, with the most serious effects found upon the respiratory system.[251] The following paragraphs describe the information used to determine the progression of Cl_2 injury in the absence of medical treatment. The sources are primarily government reports and case reports based on accidents.

Several sources,[252] some referencing other studies, generically describe mild and non-disabling Cl_2 injury symptoms—corresponding with the mild Injury Profile. "Chlorine

250 Jerris R. Hedges and William L. Morrissey, "Acute Chlorine Exposure," *Journal of the American College of Emergency Physicians* 8, no. 2 (1979): 59–63.

251 The Major Hazards Assessment Panel (MHAP), *Chlorine Toxicity—Monograph* (Rugby, UK: Institution of Chemical Engineers, 1988).

252 National Research Council, "Chlorine"; Sommerville and Channel, *Proposed Provisional Human Toxicity Estimates for Military Operations—Chlorine*; Norman A. Eisenberg, Cornelius J. Lynch, and Roger J. Breeding, *Vulnerability Model: A Simulation System for Assessing Damage Resulting from Marine Spills*, CG-D-136-75 (Rockville, MD: Environ Control Incorporated, June 1975); Agency for Toxic Substances and Disease Registry, *Toxicological Profile for Chlorine* (Atlanta, GA: ATSDR, November 2010); C. H. Beebe, *Important Constants of Fourteen Common Chemical Warfare Agents*, EA-CD-328 (Edgewood Arsenal, MD: U.S. War Department, Chemical Warfare Service, 1 December 1924).

gives evidence of instantaneous reactivity along the respiratory tract,"[253] and symptoms can therefore emerge immediately upon exposure, even at a mild dosage.[254] Similar to the respiratory tract, the eyes also react immediately to chlorine exposure.[255] Nausea is another symptom that can appear immediately to within minutes of exposure.[256] The mild effects will cease as exposure ceases, while at higher exposure levels, certain inflammatory responses would continue even after a person leaves the exposure area.[257] Since *AMedP-7.5* defines time zero in its human response models as the time at which exposure ends, the onset of mild respiratory and ocular irritation and nausea occurs at time zero.

For those exposed to mild or moderate dosages of Cl_2 and experiencing respiratory symptoms consistent with an obstructive airway pattern, this "aspect generally resolves within 30 days and most commonly within six hours."[258] The wide range of time is noteworthy, but we chose to use 6 hours since it is the most common time and is supported by data from accidental Cl_2 gas leaks that resulted in mild symptoms.[259] Thus, 6 hours is the time at which respiratory symptoms recede from Injury Severity Level 1 to Injury Severity Level 0 in the Cl_2 Mild Injury Profile.

Moderate symptoms are more severe irritation of the eyes, nose, and throat, including coughing, chest pain, and frank shortness of breath,[260] and these symptoms also appear immediately. The Bombay incident of the accidental Cl_2 gas leak at a chemical factory caused all of the 88 exposed individuals to experience immediate dyspnea, coughing, irritation of the throat and eyes, headache, giddiness, chest pain, and abdominal

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253 Ireland, *Medical Aspects of Gas Warfare*, 83.

254 The Major Hazards Assessment Panel (MHAP), *Chlorine Toxicity*, 8; Hedges and Morrissey, "Acute Chlorine Exposure," 60; Sexton and Pronchik, "Chlorine Inhalation," 90.

255 The Major Hazards Assessment Panel (MHAP), *Chlorine Toxicity*, 8; Hedges and Morrissey, "Acute Chlorine Exposure," 60.

256 Hedges and Morrissey, "Acute Chlorine Exposure," 60; Paul J. Vinsel, "Treatment of Acute Chlorine Gas Inhalation with Nebulized Sodium Bicarbonate," *Journal of Emergency Medicine* 8, no. 3 (1990): 327.

257 Chris Winder, "The Toxicology of Chlorine," *Environmental Research* 85, no. 2 (2001): 59–184.

258 Sexton and Pronchik, "Chlorine Inhalation," 90.

259 Mustafa Sever et al., "Accidental Chlorine Gas Intoxication: Evaluation of 39 Patients," *Journal of Clinical Medical Research* 1, no. 5 (2009): 274–279, 275; Rita Mrvos, Bonnie S. Dean, and Edward P. Krenzelok, "Home Exposures to Chlorine/Chloramine Gas: Review of 216 Cases," *Southern Medical Journal* 86, no. 6 (1993): 656.

260 U.S. Chemical Safety and Hazard Investigation Board (USCSHIB), Investigation Report: Chlorine Release, July 20, 2003 (7 Injured); Contaminated Antimony Pentachloride Exposure, July 29, 2003 (1 Killed); Hydrogen Fluoride Release, August 3, 2003 (1 Exposed, 1 Injured), Report No. 2003-13-I-LA (Baton Rouge, LA: Honeywell International, Inc., August 2005), 60; Vinsel, "Treatment of Acute Chlorine Gas Inhalation," 327; Henry Bunting, "The Pathological Physiology of Acute Chlorine Poisoning," in Fasciculus on Chemical Warfare Medicine—Volume II: Respiratory Tract, ed. National Research Council, Committee on Treatment of Gas Casualties (Washington, DC: National Academy of Sciences, 1945), 41.

discomfort.[261] Unfortunately, the report does not provide information about the duration of these injuries.

Another accidental Cl_2 leak caused a group of patients to experience moderate symptoms, including dyspnea, moderate cough, palpitation, tachycardia, and tachypnea, and these patients were treated and observed in the hospital for 6 to 24 hours.[262] Based on the accidental Cl_2 report, we use 24 hours as the total recovery time after suffering from moderate effects of Cl_2 exposure. The time spent at each Injury Severity Level is arbitrarily evenly split over the total time of recovery. Moderate symptoms recede from Injury Severity Level 2 to Injury Severity Level 1 in 12 hours and then to Injury Severity Level 0 in the next 12 hours.

One distinguishing feature of the Cl_2 Severe Injury Profile is that the severe effects are delayed several hours.[263] A report on the accidental Cl_2 leak that occurred in Bombay noted that "immediate effects of chlorine gas toxicity include inflammation of conjunctivae, nose, pharynx, larynx, trachea, and bronchi. After 2–3 hours, delayed effects follow in the airway mucosa."[264] Given the nonspecific language of "several" hours, we chose to use 2 hours until onset of Injury Severity Level 3 symptoms (pulmonary edema). The choice is weighted toward faster onset to err on the conservative side. However, before the onset of pulmonary edema, casualties will also suffer the symptoms associated with the Cl_2 Moderate Injury Profile. There is no indication that the non-respiratory symptoms become any more pronounced in the few hours before the onset of pulmonary edema, which dominates the clinical picture, and therefore the Injury Profile, once it occurs.

The literature indicates that respiratory symptoms improve over a period of several days when supportive care is provided. For example, an account describing clinical findings from soldiers exposed to Cl_2 during WWI states, "Patients who survived the acute effects of gassing presented the foregoing [severe] symptoms for about thirty six hours, at which time they fell asleep and subsequently awakened feeling much better," and the "rales

261 Shroff, Khade, and Srinivasan, "Respiratory Cytopathology," 28.

262 Sever et al., "Accidental Chlorine Gas Intoxication," 275.

263 The Major Hazards Assessment Panel (MHAP), *Chlorine Toxicity*, 8; Anthony M. Burda and Todd Sigg, "Pharmacy Preparedness for Incidents Involving Nuclear, Biological, or Chemical Weapons," in *Toxico-Terrorism: Emergency Response and Clinical Approach to Chemical, Biological, and Radiological Agents*, ed. Robin B. McFee and Jerrold B. Leikin (New York: McGraw Hill Medical, 2008), 222; Mary A. Wenck et al., "Rapid Assessment of Exposure to Chlorine Released from Train Derailment and Resulting Health Impacts," *Public Health Reports* 122, no. 6 (2007): 790; Gerald F. O'Malley, "Chlorine Toxicity," updated September 16, 2013, http://emedicine.medscape.com/article/832336-overview#a7.

264 Shroff, Khade, and Srinivasan, "Respiratory Cytopathology," 30.

in the chest subsequently disappeared in a few days."[265] Other more recent reports of hospitalization after chlorine exposure[266] are roughly consistent with "a few days." Although we do not have data on untreated casualties, it seems reasonable to assume that supportive care accelerated recovery.

Another article documenting the effects of exposure to Cl_2 following a 2005 South Carolina train derailment found that in "most patients, [symptoms] quickly resolved during hospitalization, suggesting that with appropriate supportive care, patients critically ill with chlorine exposure can often be discharged within a relatively short period."[267] For this incident, the "median duration of hospitalization was 4 days (range 1 to 29 days)."[268] Using this set of human data to derive the duration of the Severe Injury Profile without any form of medical treatment would not be completely accurate since supportive care was provided to the patients. Since there are no human or animal data on the duration of severe effects after Cl_2 exposure, we arbitrarily chose 7 days as the duration. This longer duration—compared to the indicated median of 4 days—is to account for the lack of supportive care since the literature suggests that supportive care might shorten the duration of symptoms; however, the specific value of 7 days is arbitrarily chosen and can be revised if other data emerge. Since no finer detail on the timing of recovery from various symptoms is available in the literature, the Cl_2 Severe Injury Profile abruptly changes from Injury Severity Level 3 to Injury Severity Level 0 at 7 days.

For the Cl_2 Very Severe Injury Profile, the respiratory symptoms again dominate the clinical picture and Injury Profile. For acute exposure to high levels of Cl_2, "in the vast majority, pulmonary edema appears at once with the resulting picture of deep cyanosis, dyspnea, and the production of large quantities of frothy fluid."[269] Many of the incidents of Cl_2 gas exposure documented in the literature did not result in deaths; however, two

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265 Henry Bunting, "Clinical Findings in Acute Chlorine Poisoning," in *Fasciculus on Chemical Warfare Medicine—Volume II: Respiratory Tract*, ed. National Research Council, Committee on Treatment of Gas Casualties. (Washington, DC: National Academy of Sciences, 1945), 60–61.

266 Walter J. Decker, "Chlorine Poisoning at the Swimming Pool Revisited: Anatomy of Two Minidisasters," *Veterinary and Human Toxicology* 30, no. 6 (1988): 584–585; Sexton and Pronchik, "Chlorine Inhalation"; David G. Bell, "Severe Lung Injury Following Exposure to Chlorine Gas: A Case Series," *Chest* 132, no.4 (2007): 566S; E. Benjamin and J. Pickles, "Chlorine-Induced Anosmia. A Case Presentation," *Journal of Laryngology and Otology* 111, no. 11 (1997): 1075–1076; David van Sickle et al., "Acute Health Effects after Exposure to Chlorine Gas Released after a Train Derailment," *American Journal of Emergency Medicine* 27, no. 5 (2009): 1–7; Edward H. Chester et al., "Pulmonary Injury Following Exposure to Chlorine Gas," *Chest* 72, no. 2 (1977): 247–250; Wenck et al., "Rapid Assessment."

267 van Sickle et al., "Acute Health Effects after Exposure to Chlorine," 5.

268 Ibid., 1.

269 Bunting, "Clinical Findings," 65.

incidents in particular did provide data regarding the speed at which death occurs.[270] In an incident during the cleaning of a wastewater holding tank at a chicken hatchery, two workers were pronounced dead upon arrival at the hospital. An autopsy of one of the individuals "reveal[ed] marked pulmonary edema and hemorrhage with desquamative loss of bronchial mucosa. Mild vascular congestion was noted in the brain, but other organ systems were unremarkable. The cause of death was listed as hemorrhagic pneumonitis due to acute chlorine exposure."[271] Of nine deaths attributed to the 2005 South Carolina train derailment, "most of the deaths from acute chlorine exposure occurred within the first hours after exposure."[272] The speed with which death can occur is further defined by WWI experience that "[s]oldiers dying within two hours were found to have completely airless, edema-filled lungs."[273] Based loosely on the preceding, the Very Severe Injury Profile begins with instant Injury Severity Level 3 symptoms, followed by escalation to Injury Severity Level 4 at 2 hours, and death in another 15 minutes.

Table 81 shows the complete Cl_2 Injury Profiles for all four severity levels. Recognizing the arbitrariness of some of the exact times used, we again remind the reader that since *AMedP-7.5* uses 1-day time resolution, many of the arbitrary decisions will have no net effect on estimates produced by *AMedP-7.5*.

270 van Sickle et al., "Acute Health Effects after Exposure to Chlorine"; Vivian Auerbach and Claire Hodnett, "Neuropsychological Follow-up in a Case of Severe Chlorine Gas Poisoning," *Neuropsychology* 4, no. 2 (1990): 105–112.

271 Auerbach and Hodnett, "Neuropsychological Follow-Up," 106.

272 van Sickle et al., "Acute Health Effects after Exposure to Chlorine," 5.

273 Bunting, "The Pathological Physiology," 45.

Table 81. Inhaled Cl_2 Injury Profiles

Time Point (min)	Cl_2 Mild	Cl_2 Moderate	Cl_2 Severe	Cl_2 Very Severe
1	1	2	2	3
120	1	2	3	4
135	1	2	3	4[a]
360	0	2	3	
720	0	1	3	
1440	0	0	3	
10080	0	0	0	

[a] Death is modeled to occur at this point, based on the default value of the parameter $T_{death\text{-}CN\text{-}SL4}$ in *AMedP-7.5*.

Medical Treatment (*AMedP-7.5 Table 4-33*)

5. Efficacy of Medical Treatment

No antidote is available for Cl_2 poisoning.[274] The literature does not provide information suitable for estimating a protection factor related to medical treatment (PF_{MT}) based on treatment for Cl_2 injuries. In fact, some argument surrounds the efficacy of corticosteroids, beta-adrenergic agonists, and sodium bicarbonate.[275] It is clear, however, that as a whole, medical treatment significantly improves the prognosis of anyone exposed to life-threatening Cl_2 dosages.

A report on the health effects of the derailment of a train carrying Cl_2 states that of 25 people admitted to the intensive care unit (ICU), only 1 died.[276] A report describing the care of nine adult males who were exposed to Cl_2 by a vehicle-borne improvised explosive device (VBIED) states that eight of the nine survived, but they required intubation.[277] Based on the necessity of treatment in the ICU (in the former incident) and intubation (in the latter incident), we assume that all 34 cases were life-threatening, which correlates with the Very Severe Injury Profile. Grouping these incidents together gives a fatality rate of 2/34 for Very Severe patients. Since there are no data on dosage in these 34 cases that could potentially allow the estimation of PF_{MT}, the efficacy of medical treatment is included by reducing the lethality rate to 2/34, or 6%, for the Very Severe Injury Profile. This approach lacks the intrinsic defeat dose of the PF_{MT} model and may result in an underestimate of fatalities in cases of very high exposure.

274 Burda and Sigg, "Pharmacy Preparedness," 222.

275 Burda and Sigg, "Pharmacy Preparedness," 222; Sexton and Pronchik, "Chlorine Inhalation," 91; James W. Rhee, "Pulmonary Agents," in *Toxico-Terrorism: Emergency Response and Clinical Approach to Chemical, Biological, and Radiological Agents*, ed. Robin B. McFee and Jerrold B. Leikin (New York: McGraw Hill Medical, 2008), 299; Meyers, "Chlorine Inhalation," 585; Vinsel, "Treatment of Acute Chlorine Gas Inhalation," 328.

276 van Sickle et al., "Acute Health Effects after Exposure to Chlorine," 3.

277 Bell, "Severe Lung Injury."

As discussed below, for nonlethal dosages, modern medical treatment appears to have little effect on the time until a soldier could RTD.

6. MTOR Table

Table 82 is the MTOR table for Cl_2 casualties. It is derived from the Injury Profiles and RTD and DOW estimates from clinical case reports. See the paragraphs after Table 82 for discussion.

Medical treatment comprises supportive care with forced bed rest, which is effective at preventing death but has little effect on the total recovery time in patients who did not need intensive care. For the Very Severe Injury Profile, the fatality rate is reduced.

In the discussions below, which explain the other parts of Table 82, the potential for administrative declaration of asymptomatic "casualties" or delay of RTD for additional monitoring is ignored, consistent with the limitation discussed in Section 0.

Table 82. Cl_2 Medical Treatment Outcome Reporting

Injury Profile	DOW[a]	CONV[a]	RTD[a]
Cl_2 Mild	0%	0%	Day 2: 100%
Cl_2 Moderate	0%	0%	Day 2: 100%
Cl_2 Severe	0%	0%	Day 5: 100%
Cl_2 Very Severe	Day 2: 7%	Day 7: 27% Day 14: 22% Day 21: 22% Day 28: 22%	Day 60: 93%

[a] Reported values indicate the fraction that changes status on a given day; they are not cumulative.

Casualties in the Cl_2 Mild and Moderate cohorts will recover spontaneously and be able to RTD after 6 hours and 24 hours, respectively. Therefore, individuals in either cohort will recover sufficiently to RTD on Day 1, so they are reported as RTD on Day 2 in the MTOR. The availability of medical treatment has no effect on recovery for these Injury Profiles.

Individuals in the Severe Injury Profile cohort will take longer to recover, but with supportive care, the recovery time will likely be shortened. The WWI accounts[278] and more recent clinical case reports[279] indicate that recovery generally occurs over a few days, and, "with appropriate supportive care, patients critically ill with chlorine exposure can often

278 Bunting, "Clinical Findings," 60–61.

279 Decker, "Chlorine Poisoning"; Sexton and Pronchik, "Chlorine Inhalation"; Bell, "Severe Lung Injury"; Benjamin and Pickles, "Chlorine-Induced Anosmia"; van Sickle et al., "Acute Health Effects after Exposure to Chlorine," Chester et al., "Pulmonary Injury"; Wenck et al., "Rapid Assessment."

be discharged within a relatively short period."[280] The duration of the severe Cl_2 injuries without medical treatment is modeled as 7 days. When given supportive care, symptoms are assumed to ameliorate sufficiently in 4 days. RTD is reported on Day 5 in the MTOR. An assumption was used here because no specific data were available to make a better supported model.

The literature did not support an estimate of PF_{MT} to represent the effect of medical treatment on otherwise lethal Cl_2 injuries (i.e., for the Cl_2 Very Severe cohort). As described in Subsection 1.B.5, based on two reports covering a combined 34 cases that would have been lethal without medical treatment, the model includes the efficacy of medical treatment by reducing the lethality rate for individuals in this cohort to 6%. For casualties who die, the model uses the time until death based on the duration of illness without medical treatment, which depicts DOW in the third hour and is reported in the MTOR as Day 2.

Since the Cl_2 Very Severe cohort is lethal without medical treatment, the most relevant case reports for developing an RTD estimate are those in which intensive care or intubation was necessary to sustain the life of the patient. The two reports used to estimate the fatality rate also provide information matching this criterion. The VBIED report states that the mean number of days for which the eight surviving patients required mechanical ventilation was 8.1 days[281] but does not state the average time until discharge from the hospital. The train derailment report states that 24 of the 25 victims who were admitted to the ICU survived. The median length of ICU stay was 3 days, with an interquartile range of two to 5.5 days. Those who were intubated spent a median of 6 days on the ventilator, with an interquartile range of 3 to 12 days. Information on total length of hospital stay includes those who were not admitted to the ICU. The 70 people who were discharged alive spent a median of 4 days in the hospital, with an interquartile range of 2 to 6 days and a range of 1 to 29 days.[282]

One question to consider is, what does hospital discharge mean in terms of *AMedP-7.5*? The train derailment report includes a section on medications given to patients at discharge, suggesting that they were not fully recovered. It also states, as a general comment (not applied to the specific patients), that most people recover within "months."[283] Thus, we will use the hospital discharge times as estimates of when casualties become CONV and model RTD at 2 months for all Very Severe Cl_2 casualties.

280 van Sickle et al., "Acute Health Effects after Exposure to Chlorine," 5.

281 Bell, "Severe Lung Injury."

282 van Sickle et al., "Acute Health Effects after Exposure to Chlorine, "4.

283 Ibid., 6.

It is reasonable to assume that the longest hospital stay was associated with someone who had spent time in the ICU. It also seems that even after an ICU stay of 2 days, it is unlikely that a person would be discharged before the end of the first week. To represent the approximate range of hospitalization time without making an overly detailed model, we have arbitrarily split the 93% modeled to survive between days 7, 14, 21, and 28 (weighted heavier at 7 days to match the VBIED data).

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1.10. NH_3 Model
(*AMedP-7.5 Section 4.2.10*)

Introduction

NH_3 is the third most abundantly produced toxic industrial compound in the world.[284] It is a strong irritant and corrosive that is toxic to humans in almost all exposure scenarios. Its odor threshold of 3.5–35 mg/m^3 (5–50 parts per million (ppm))[285] is sufficiently low to provide sensory warning of its presence. However, NH_3 causes olfactory fatigue or adaptation, making its presence difficult to detect when exposure is prolonged. Thus, the odor threshold may extend up to 37 mg/m^3 (53 ppm) according to the Agency for Toxic Substances and Disease Registry (ATSDR).[286]

The objective of this chapter is to describe the human response model for NH_3 as it has been incorporated into *AMedP-7.5*. The chapter first discusses a scoping assumption. Then it describes the physiological effects of NH_3, the toxicity parameters used in *AMedP-7.5*, development of Injury Profiles, and the medical treatment model.

Assumption (*AMedP-7.5 Section 4.2.10.2*)

> **Assumption**: Percutaneous exposure to NH_3 vapour and liquid are negligible.

Liquid ammonia is unlikely to be present in a battlefield scenario because of its low boiling point, –33.3 °C. Any liquid ammonia that is present is therefore a cold hazard, which is beyond the scope of *AMedP-7.5*. Further, none of the sources we consulted in developing this model discussed toxicity of NH_3 vapor to the skin.

Physiological Effects (*AMedP-7.5 Table 4-34*)

NH_3 causes damage mainly in the respiratory system. Although NH_3 rapidly enters the eye, causing local irritation and corrosive injuries, systemic absorption through the eye is not considered to be quantitatively significant.[287] Damage to the respiratory system when in contact with NH_3 is proportional to the depth of inhalation, duration of exposure, and concentration and pH of the gas or liquid.[288] Following a short-term inhalation exposure, NH_3 is almost entirely retained in the upper nasal mucosa. The main clinical effects of large

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284 Igor Makarovksy et al., “Ammonia – When Something Smells Wrong,” *Israel Medical Association Journal* 10, no. 7 (July 2008): 537.

285 Douglas. R. Sommerville et al., *Review and Assessment of Ammonia Mammalian Lethality Data and the Development of a Human Estimate*, CBRNIAC-SS3-829-1 (Aberdeen Proving Ground, MD: Chemical Security Analysis Center, Department of Homeland Security, 2011), 5-4.

286 Agency for Toxic Substances and Disease Registry (ATSDR), “Toxicological Profile for Ammonia,” last updated January 21, 2015, http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=11&tid=2.

287 Makarovksy et al., “Ammonia – When Something Smells Wrong,” 538.

288 Ibid.

exogenous exposure to NH_3 include non-disabling reversible effects manifested by irritation to the eyes, throat, and nasopharyngeal region of the respiratory tract.[289] Inhalation of high concentrations of NH_3 or long-term exposure to NH_3 might cause severe damage to the respiratory tract, particularly in the tracheobronchial and pulmonary regions, and might lead to systemic absorption through the lungs.[290] The time during which symptoms begin to manifest is directly correlated to the exposure concentration. A higher exposure dose results in quicker appearance of symptoms. People who are able to escape the affected environment are usually not subjected to severe injuries. Furthermore, the absence of symptoms following inhalational exposure to NH_3 essentially rules out significant injury.

Clinical Manifestations of Acute NH_3 Exposure

The clinical manifestations of acute NH_3 exposure are usually immediate, and its toxic effects are mediated through its irritant and corrosive properties. NH_3 is an upper respiratory tract irritant, and its inhalation rapidly causes irritation to the nose, throat, and respiratory tract. Increased lacrimation and respiratory rate, coughing, and respiratory distress may occur. Retention of NH_3 at low concentrations in the nasal mucosa may protect against some lung effects. Substantial exposures to concentrated aerosols of ammonium hydroxide (NH_4OH) and elevated levels of NH_3 gas or anhydrous NH_3 fumes can cause burns at all depths in the oral cavity, nasopharynx, larynx, and trachea, together with airway obstruction, respiratory distress, and pulmonary edema.[291] Exposure to a massive concentration of NH_3 gas may be fatal within minutes, and asphyxiation may occur after exposure in poorly ventilated or enclosed spaces. Findings in fatal cases include extensive edema, full-thickness burns to the entire respiratory tract, purulent bronchitis, and greatly distended lungs.[292] The bronchial walls may be stripped of their epithelial lining.[293]

Following ocular exposure, initial symptoms include increased production of tears, a burning sensation, blepharospasm, conjunctivitis, and photophobia. At higher

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289 National Research Council, *Acute Exposure Guideline Levels for Selected Airborne Chemicals*, vol. 6 (Washington, DC: The National Academies Press, 2008), 60.

290 Ibid.

291 Lanny Garth Close, Francis L. Catlin, and Arnold M. Cohn, "Acute and Chronic Effects of Ammonia Burns on the Respiratory Tract," *Archives of Otolaryngology* 106, no. 3 (March 1, 1980): 151–158; Craig E. Amshel et al., "Anhydrous Ammonia Burns: Case Report and Review of the Literature," *Burns* 25, no. 5 (1 August 2000): 493–497.

292 S. K. Price et al., "Fatal Ammonia Inhalation. A Case Report with Autopsy Findings," *South African Medical Journal* 64, no. 24, (December 3, 1983): 952–955; G. Woto-Gaye et al., "Death from Ammonia Poisoning: Anatomo-Pathologic Features," *Dakar Médical* 44, no. 2 (January 1999): 199–201.

293 D. Ludec et al., "Acute and Long Term Respiratory Damage Following Inhalation of Ammonia," *Thorax* 47, no. 9 (September 1992): 755–757; 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.

concentrations, corneal ulcerations, iritis, anterior and posterior synechia, corneal opacification, cataracts, glaucoma, and retinal atrophy may develop. Permanent eye damage can occur as a result of tissue destruction and elevations in intraocular pressure.[294]

Systemic effects following acute exposure to high concentrations of NH_3 include an elevated pulse and blood pressure, bradycardia, cardiac arrest, cyanosis, hemorrhagic necrosis of the liver, cerebral edema, seizures, and coma.

Mechanism of Toxicity and Pharmacology

NH_3 is extremely soluble in water and dissolves in the mucous fluid covering the mucous lining of the respiratory system to produce NH_4OH, a strong base. The reaction is exothermic in nature and may inflict significant thermal injury. NH_4OH causes severe alkaline chemical burns to the skin, the eyes, and especially the respiratory system. Mild exposure primarily affects the upper respiratory tract, while more severe exposure tends to affect the entire respiratory tract.

Tissue damage from NH_4OH is caused by liquefaction necrosis and penetrates far deeper than the damage caused by an equipotent acid. In the case of ammonium, the tissue breakdown liberates water, thus bringing about the conversion of NH_3 to NH_4OH. In the respiratory tract, this process results in the destruction of the cilia and the mucosal barrier, leading to infection. Moreover, secretions, sloughed epithelium, cellular debris, edema, and reactive smooth muscle contractions cause significant airway obstruction. Airway epithelium can regain barrier integrity within 6 hours after exposure if the basal cell layer remains intact. However, damaged epithelium is often replaced by granular tissue, which may be one of the causes of chronic lung disease following NH_3 inhalation injury.

Systemically absorbed NH_3 is well distributed throughout the body compartments and reacts with hydrogen ions, depending on the pH of the compartment, to produce ammonium ions (NH_4+). These ammonium ions are endogenously produced in the gut from the bacterial breakdown of nitrogenous constituents of food. Almost all this endogenous ammonium is absorbed by passive diffusion from the intestinal tract before entering the hepatic portal vein. In the liver, ammonium ions are extensively metabolized to urea and glutamine. Consequently, the levels of NH_3 that reach the circulatory system are low.

NH_3 reaching the circulatory system is excreted by humans as urinary urea. Small amounts of NH_3 are excreted via urine. The average daily excretion for humans is approximately 2–3 μg, about 0.01% of the total body burden. Small amounts of unabsorbed NH_3 may also be excreted from gastrointestinal tract in the feces.

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294 Ann Welch, “Exposing the Dangers of Anhydrous Ammonia,” *The Nurse Practitioner* 31, no. 11 (November 2006): 40–45.

Table 83 summarizes the preceding qualitative descriptions in a format amenable to use in *AMedP-7.5* and for the analysis presented in this chapter. Consistent with the definition of Injury Profile, the symptom sets are clinically differentiable. The next part of the model derivation is to define four sets of toxicity parameters, each associated with a *peak* Injury Severity Level equal to one of the four levels defined in Table 83.

Table 83. Association of NH_3 Injury Severity Levels with NH_3 Symptom Sets

Injury Severity Level	Set of Symptoms
0	No observable injury
1 (mild)	Mild eye irritation, rhinorrhea, cough, sneezing, drooling, dyspnea, headache
2 (moderate)	Tear production, burning sensation, blepharospasm, conjunctivitis, photophobia, more pronounced cough, pharyngitis, laryngitis, moderate throat irritation
3 (severe)	Corneal ulcerations, iritis, anterior and posterior synechia, corneal opacification, cataracts, glaucoma; retinal atrophy, directly caustic to airway, laryngospasm, bronchospasm, chest pain, loss of consciousness
4 (very severe)	Sloughing and necrosis of airway mucosa, severe chest pain, pulmonary edema, respiratory failure, cerebral edema, seizures, coma, death

Toxicity Parameters (*AMedP-7.5 Table 4-34*)

We believe that the toxicity parameter estimates from CSAC are the best available, and since the CSAC NH_3 report is *not* FOUO, we used its estimates where possible (see Subsection 1.B.8). CSAC estimated that the median lethal dosage (concentration time) (LCt_{50}) is 67700 mg-min/m^3 for a 2-minute exposure in the healthy population.[295] Since CSAC did not report on the ECt_{50}-severe value, we used the ECt_{50}-severe value of 7800 mg-min/m^3 reported in ECBC-TR-856 for a 2-minute exposure in the healthy population.[296]

Although the CSAC report and ECBC-TR-856 use overlapping sources to derive the reported values, CSAC used six sources published post-1962 to calculate the weighted average of the PS while ECBC-TR-856 only used five of the six sources to determine the weighted average of the PS. Therefore, the PS from the two sources differ. The PS for NH_3 reported by CSAC is 16.5; the PS reported by ECBC-TR-856 is 17; *AMedP-7.5* uses a PS of 16.5 for the lethal level of effect.

295 Sommerville et al., *Review and Assessment of Ammonia*, 6-3.

296 Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*, 26.

The CSAC report on CK states that since severe effects and lethality follow the same toxic mechanism, the PSs should be the same.[297] This principle can also be applied to other agents and other levels of effect as long as the same toxic mechanism is still at work. Since the mechanism of NH_3 toxicity does not vary by severity of injury, we assumed that the mild, moderate, and severe PSs are equal to the lethal PS. This assumption also helps avoid illogical results, such as two toxicity curves intersecting. For all levels of effect, we use 16.5 as the estimated PS.

Reports on accidental exposure to NH_3 that caused nonlethal effects are plentiful in the literature; however, none of the studies contained quantitative exposure data. Our literature review identified only a handful of reports on low-level toxicity study of NH_3 in humans that can be used for estimating mild and moderate toxicity parameters for this paper. Table 84 lists the human data that were gathered from four studies that we considered. Each study described the symptoms experienced by the exposed subjects when exposed to NH_3 over durations of equal to or greater than 5 minutes. We were unable to acquire two of the studies (Industrial Bio-Test Lab (1973) and MacEwen et al. (1970)), but we obtained the data from a report by Sommerville, who described the symptoms experienced by the exposed individuals to the low levels of NH_3 as "mild."[298] Since most of the data have an exposure duration of equal to or greater than 5 minutes and NH_3 has a toxic load exponent of greater than 1 (n = 2.0),[299] we deemed it necessary to use EPD calculations in an attempt to compensate for the data, which were only from relatively long durations of exposure. Calculating dosages without accounting for toxic load effects yields meaningless dose values when compared to the lethal and severe toxicity estimates.

Using the EPD formula given in Subsection 0, we calculated the estimated human EPD (see Table 85). Based on the data, the estimated EPD range of 71–111 mg-min/m^3 caused exposed individuals to detect the odor and experience nasal dryness and possibly a faint irritation to the eyes, nose, throat, and chest. These resulting symptoms are less severe than Injury Severity Level 1 (mild) symptoms shown in Table 83; therefore, we conclude that exposure to a dose less than or equal to 111 mg-min/m3 will produce "no observable symptoms." The next estimated EPD range between 157 and 542 mg-min/m^3 caused NH_3-exposed patients to smell a highly intense odor and experience mild general discomfort, with moderate irritation to the eyes, nose, throat, and chest, and a mild urge to cough. These symptoms correlate to the Injury Severity Level 1 (mild) listed in Table 83. The estimated EPD range between 596 and 843 mg-min/m3 caused NH_3-exposed individuals to

297 Sommerville et al., *Review and Assessment of Cyanogen Chloride*, B–11. This principle is also applied for several agents in Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*.

298 Sommerville et al., *Review and Assessment of Ammonia*, 4-2.

299 Ibid., 6-2. In the source, this value is derived from lethal effects and then applied to other levels of effect.

experience moderate irritation to eyes, nose, throat, and chest; a mild urge to cough; and moderate general discomfort. We associated this range with an apparent Injury Severity Level between 1 and 2. The next estimated EPD range (868–1193 mg-min/m^3), which is associated with an apparent Injury Severity Level 2 (moderate), caused individuals to experience highly intense irritation to the eyes, nose, throat, and chest; a highly intense urge to cough; and moderate discomfort. The estimated EPD range between 1518 and 1917 mg-min/m^3 caused highly intense irritation to the eyes, nose, throat, and chest; a highly intense urge to cough; lacrimation; hyperventilation; and unbearable general discomfort. Such symptoms are correlated to an Injury Severity Level between 2 and 3.

Table 84. Relevant Nonlethal Inhalational Exposures to NH_3

Source	Inhaled CT (mg-min/m^3)	Exposure Duration (min)	Symptoms	Apparent Injury Severity Level
Industrial Bio-Test Laboratories, Inc.	112–175	5	Nasal dryness	0
	252–500	5	Nasal, eye, throat, and chest irritation, lacrimation	1
MacEwen, Theodore, and Vernot	210	10	Odor moderately intense to highly penetrating; irritation faint or not detectable	0
———	350	10	Highly penetrating odor, mild irritation	0–1
Verberk	1050	30	Moderately intense odor, moderate irritation to the eyes, nose, throat and chest; mild urge to cough; slight general discomfort	1
———	2100	60	Highly intense odor; moderate irritation to eyes, nose, throat, and chest; mild urge to cough; slight general discomfort	1
———	1680	30	Highly intense odor; highly intense eye and nose irritation; moderate throat and chest irritation; mild urge to cough; moderate general discomfort	1
———	4200	120	Offensive odor; moderate irritation to eyes, nose, throat, and chest; mild urge to cough; mild general discomfort	1
———	2310	30	Highly intense odor; moderate irritation to eyes, nose, throat and chest; mild urge to cough; moderate general discomfort	1–2
———	3360	60		1–2
———	2940	30		1–2
———	4620	60		1–2
———	6720	120	Highly intense odor; highly intense eye, nose, throat and chest irritation;	2

Source	Inhaled CT (mg-min/m^3)	Exposure Duration (min)	Symptoms	Apparent Injury Severity Level
			moderate urge to cough; moderate general discomfort	
———	5880	60	Highly intense odor; unbearable eye, nose, throat and chest irritation; moderate urge to cough; moderate general discomfort	2
———	9240	120	Highly intense odor; highly intense eye, nose, throat and chest irritation; urge to cough; general discomfort	2
———	11760	120	Highly intense odor; highly intense eye, nose, throat and chest irritation; highly intense urge to cough; and unbearable general discomfort	2–3
Silverman, Whittenberger, and Muller	5250	15	Nose and throat irritation, nasal dryness and stuffiness; excessive lacrimation; hyper-ventilation; unbearable – subjects unable to continue exposure to specified concentration	2–3

Note: See Appendix B for full reference citations.

Table 85. Estimated Human EPDs from Table 84 Data

Source	Inhaled CT (mg-min/m^3)	Exposure Duration (min)	EPD-Adjusted Dose (mg-min/m^3)	Apparent Injury Severity Level
Industrial Bio-Test Laboratories, Inc.	112–175	5	71–111	0
	252–500	5	159–317	1
MacEwen, Theodore, and Vernot	210	10	94	0
———	350	10	157	0–1
Verberk	1050	30	271	1
———	2100	60	383	1
———	1680	30	434	1
———	4200	120	542	1
———	2310	30	596	1–2
———	3360	60	613	1–2
———	2940	30	759	1–2
———	4620	60	843	1–2
———	6720	120	868	2

Source	Inhaled CT (mg-min/m^3)	Exposure Duration (min)	EPD-Adjusted Dose (mg-min/m^3)	Apparent Injury Severity Level
———	5880	60	1074	2
———	9240	120	1193	2
———	11760	120	1518	2–3
Silverman, Whittenberger, and Muller	5250	15	1917	2–3

Note: See Appendix B for full reference citations.

Several options are available for using the six estimated EPDs that led to mild symptoms to estimate the ECt_{50}-mild. Seemingly reasonable options include the average of the values, the median of the values, and the average of the highest and lowest values. Since no metric is available for determining which strategy is best, we arbitrarily chose the latter, which gives the estimated ECt_{50}-mild of 350 mg-min/m^3.

The three estimated EPDs that caused moderate symptoms can also be evaluated in the same way to estimate the ECt_{50}-moderate. The average of the highest and lowest values gives the estimated ECt_{50}-moderate of 1000 mg-min/m^3 (rounded from 1031 mg-min/m^3). We recognize that this method of estimating toxicity parameters may not be the most accurate but found no other option. Therefore, as better data become available, the estimated ECt_{50}-mild and ECt_{50}-moderate should be updated accordingly.

Table 86 summarizes the set of median toxicities and PSs for Inhaled NH_3.

Table 86. Median Toxicities and Probit Slopes for Inhaled NH_3

Injury Profile	Effect	Median Toxicity[a] (mg-min/m^3)	Probit Slope (Probits/Log (dose))
NH_3 Very Severe	Lethal	67,700	16.5
NH_3 Severe	Severe	7,800	16.5
NH_3 Moderate	Moderate	1,000	16.5
NH_3 Mild	Mild	350	16.5

[a] The median toxicity is an estimate for a 2-minute exposure.

Injury Profiles (*AMedP-7.5 Table 4-35*)

The corrosive and exothermic properties of NH_3 can result in immediate irritation and burns to several physiological systems of the body, including respiratory, ocular, and upper gastrointestinal. The neurological and cardiac systems can develop symptoms over time as the toxic effect of NH_3 progresses after an acute exposure. The following paragraphs describe the information used to determine the progression of NH_3 injury in the absence of

medical treatment. The sources are primarily case reports based on accidents, government reports, and experimental studies.

A few sources (such as *MACW*),[300] some referencing other studies, generically describe mild and non-disabling NH_3 injury symptoms that correspond with the mild Injury Profile (e.g., "casualties with mild exposure present with pain and conjunctival and upper respiratory inflammation but no signs of respiratory distress"[301]). Lessenger noted that "patients presented with mild catarrhal symptoms including stinging of the eyes and mouth, pain on swallowing, and tightness of the throat. Vital signs in these patients were normal and the examination was normal with the exception of conjunctival and mucosal erythema. […] these people were sent home without any problems."[302] In low doses, the agent is primarily a centrally acting TIC and causes irritation when in contact with moist watery tissues of the central airways and the ocular system to rapidly form a strong alkaline solution.[303]

Since *AMedP-7.5* defines time zero in its human response models as the time at which exposure ends, the onset of mild respiratory and ocular irritation occurs at time zero. Headache is another early symptom after mild NH_3 exposure,[304] although the accounts do not generally specify a time of onset. In the absence of specific timing information related to the onset of headaches, we assumed that the onset of headaches parallels that of the other physiological systems. Individuals recover quickly and are unlikely to have delayed or long-term adverse health effects after inhaling low doses of NH_3 if they are quickly moved into fresh air.[305] Such a qualitative statement poses a difficulty in quantifying the time to recovery after a mild exposure to NH_3, but certainly implies less than 1 day. Caplin, in describing the clinical course in patients exposed to NH_3 as a result of a pierced NH_3 tank during a 1940 air-raid in London, noted that those with mild symptoms were fit to discharge after a few hours' rest, but he also pointed out that if not for the severity of air-raids in London at that time and the corresponding need to keep beds clear, most patients would have been allowed to remain a little longer.[306] Although this is still somewhat qualitative, it gives the picture of perhaps 6 hours until full recovery under normal circumstances.

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300 Tuorinsky and Sciuto, "Toxic Inhalational Injury," 339–370; James E. Lessenger, "Anhydrous Ammonia Injuries," VOLUME 3, NUMBER 3 *Journal of Agromedicine* 9, no. 2 (2005): 191–203; Makarovksy et al., "Ammonia – When Something Smells Wrong."

301 Tuorinsky and Sciuto, "Toxic Inhalational Injury," 355–356.

302 Lessenger, "Anhydrous Ammonia Injuries," 197.

303 Makarovksy et al., "Ammonia – When Something Smells Wrong."

304 Britt-Marie Sundblad et al., "Acute Respiratory Effects of Exposure to Ammonia on Healthy Subjects," *Scandinavian Journal of Work, Environment & Health* 30, no. 4 (August 2004): 313–321.

305 Makarovksy et al., "Ammonia – When Something Smells Wrong," 539.

306 Caplin's description of the mild symptoms included onjunctive and upper respiratory inflammation leading to pain in the eyes and mouth, pain upon swallowing, and tightness of the

The important point, since *AMedP-7.5* uses a reporting resolution of 1 day, is that recovery from Mild symptoms will apparently occur in less than 1 day, so individuals with Mild NH_3 injury will be RTD on Day 2 in any case. Therefore, the time at which respiratory symptoms recede from Injury Severity Level 1 to Injury Severity Level 0 in the NH_3 Mild Injury Profile is 6 hours, with the recognition that the chosen value is somewhat arbitrary but also that even if it were changed to 12 hours, it would make no practical difference in the output of *AMedP-7.5*.

Moderate symptoms are more severe irritation of the eyes, nose, and throat; more pronounced cough; chest pain; tightness of the chest; hoarseness; dysphagia; lacrimation; swelling of the eyelids; and conjunctival hyperemia.[307] These symptoms appear immediately or shortly after exposure. It has been noted that the "higher the exposure dose the sooner the symptoms will appear."[308] However, some symptoms, such as irritation of the eyes, nose, and throat, appear immediately upon exposure to NH_3.[309] Therefore, the onset of moderate symptoms is modeled at time zero. Although the recovery time after a moderate exposure to NH_3 is not specifically quantified in the literature, *MACW* states, "patients show improvement within 48 to 72 hours, and patients with mild exposure could recover fully in this time."[310]

Since evidence indicates that patients with exposures considered Mild on the *AMedP-7.5* injury severity scale recover faster, we assume that "mild" according to *MACW* corresponds more to Moderate on the *AMedP-7.5* scale. Thus, the duration of moderate symptoms is 72 hours. We were unable to find information that would allow modeling of a time at which symptoms decrease from Moderate to Mild. For the NH3 Moderate Injury Profile, the moderate symptoms begin at Injury Severity Level 2 at time zero and recede to Injury Severity Level 0 in 72 hours.

Casualties in the next Injury Severity Level (severe) experience severe health effects with frank respiratory distress, productive cough, pulmonary edema, dysphagia, slight cyanosis, and intense dyspnea.[311] At such high dosage, the exposure is great enough that NH_3 has reached the peripheral airway, resulting in peripheral effects, such as pulmonary

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throat, with little to no cough, no shock or fever or elevated pulse. This description fits well with Mild symptoms in Table 83. See Maxwell Caplin, "Ammonia-Gas Poisoning Forty-Seven Cases in a London Shelter," *The Lancet* 238, no. 6152 (July 1941): 95–96.

307 Tuorinsky and Sciuto, "Toxic Inhalational Injury and Toxic Industrial Chemicals," 356; Hurst et al., *Medical Management of Chemical Casualties*, 24; Caplin, "Ammonia-Gas Poisoning Forty-Seven Cases," 95–96.

308 Makarovksy et al., "Ammonia – When Something Smells Wrong." 539.

309 National Research Council, "Ammonia: Acute Exposure Guideline Levels," chap. 2 in vol. 6, *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (Washington, DC: National Academies Press, 2008), 59.

310 Tuorinsky and Sciuto, "Toxic Inhalational Injury and Toxic Industrial Chemicals," 356.

311 Ibid., 356; Caplin, "Ammonia-Gas Poisoning Forty-Seven Cases," 95.

edema, that begin between 2 and 24 hours after exposure. Before the onset of pulmonary edema, casualties will suffer respiratory and ocular symptoms, including chest pains, cough, intense dyspnea, lacrimation, and intense irritation of the eyes, nose, and throat. The effects of a large dose of NH_3 inhalational exposure cause immediate central effects that are followed by delayed peripheral effects. The USAMRICD Handbooks indicate that casualties who present with symptoms that lead to pulmonary edema before 6 hours after exposure will likely die even if medical treatment is provided, and casualties who present later than 6 hours after exposure will likely survive if immediate intensive medical care is provided.[312]

We propose that individuals who are exposed to a severe level of NH_3 will immediately experience onset of respiratory and ocular symptoms at Severity Level 2 at time zero. The symptoms then increase from Severity Level 2 to Severity Level 3 12 hours post-exposure to account for the onset of pulmonary edema. The change in severity levels at 12 hours was arbitrarily chosen because it isa nice round number and is roughly the midpoint between 2 and 24 hours, the range within which peripheral effects are said to begin. For the recovery time, *MACW* states that "for patients with more severe respiratory symptoms, recovery can be expected within several weeks to months."[313] Thus, *AMedP-7.5* models the Injury Severity Level 3 receding to Injury Severity Level 0 in 1 month (30 days). Intermediate steps down in severity are not modeled because there is insufficient information available—indeed, even the information supporting the changes in severity that are modeled is rather weak.

For the NH_3 Very Severe Injury Profile, victims almost instantly become unconscious and have severe chemical burns of the face, eyes, mouth, and throat. Victims may regain consciousness or drift into coma and develop clinical and radiographic features of pulmonary edema and experience respiratory distress.[314] Since such symptoms are not survivable in the absence of medical treatment, the Injury Profile ends with death at 15 minutes post-exposure, in accordance with the default value of the *AMedP-7.5* parameter $T_{death\text{-}CN\text{-}SL4}$.

Table 87 shows the complete NH_3 Injury Profiles for all four severity levels. Recognizing the arbitrary nature of some of the specific times used, we remind the reader that since *AMedP-7.5* uses 1-day time resolution for reporting, many of the arbitrary decisions will have no effect on estimates produced by *AMedP-7.5*.

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312 Hurst et al., *Medical Management of Chemical Casualties*, 31–32; Hurst et al., *Field Management of Chemical Casualties*, 60–63

313 Tuorinsky and Sciuto, "Toxic Inhalational Injury and Toxic Industrial Chemicals," 356.

314 Kass et al., "Bronchiectasis Following Ammonia Burns"; Price et al., "Fatal Ammonia Inhalation. A Case Report"; Ludec et al., "Acute and Long Term Respiratory Damage."

Table 87. Inhaled NH_3 Injury Profiles

Time Point (min)	NH_3 Mild	NH_3 Moderate	NH_3 Severe	NH_3 Very Severe
1	1	2	2	4
15	1	2	2	4[a]
360	0	2	2	
720	0	2	3	
4320	0	0	3	
43200	0	0	0	

[a] Death is modeled to occur at this point, based on the default value of the parameter $T_{death\text{-}CN\text{-}SL4}$ in *AMedP-7.5*.

Medical Treatment (*AMedP-7.5 Table 4-36*)

Efficacy of Medical Treatment

Ideally, we would quantify the efficacy of medical treatment using a protection factor due to medical treatment (PF_{MT}), which can be calculated by taking the ratio of the LD_{50} with medical treatment to the LD_{50} without medical treatment, if such data are available. Other methods of calculating PF_{MT} may be useful, depending on the data available.

Literature reports on the treatment of NH_3 poisoning in humans are primarily clinical case reports. In most of these reports, a person was or people were accidentally exposed to NH_3 gas. In such cases, the dose cannot be directly compared to the proposed untreated dosages because the dosage is unknown; when we use such data, it is on the basis of assessing the severity of the reported symptoms relate to Table 83. Case reports and the USAMRICD Handbooks do not provide any quantifiable description of the effect of medical treatment for NH_3 injuries for estimating PF_{MT}. Since no antidote is available,[315] the dosages for untreated individuals are the same as the dosages for treated individuals. Based on the case reports, it is clear that medical treatment does improve the prognosis of anyone exposed to life-threatening NH_3 dosages.

Since NH_3 is a common industrial and household chemical, it is the third most common chemical released accidentally from manufacturing or storage facilities in the United States[316] Human accidental exposure to NH_3 via inhalation makes up most of the clinical case reports found in literature (see Table 88); however, using these reports for the treated models presents a few problems. First, available data on the NH_3 levels during an accidental release are limited since in most cases, the air concentration was neither measured nor estimated. Second, in some cases, an explosion of the storage tank or fire in the nearby facilities accompanied the release of NH_3, which complicates the assessment of the damage caused by the gas leak itself.

315 Makarovksy et al., “Ammonia – When Something Smells Wrong,” 539.

316 Ibid., 542.

Table 88. Clinical Case Reports of Human Exposure to NH_3

Source	Exposure Scenario	Exposure Route	Outcome
Slot	Accident – Gas Leak	Inhalation	1 died on Day 30, 5 survived
Caplin	Accident – Gas Leak	Inhalation	13 died, 34 survived
Levy et al.	Accident – Gas Leak	Dermal, Inhalation	4 survived
Mulder et al.	Accident – Gas Leak	Inhalation	Died after 6 hours
Kass et al.	Accident – Gas Leak	Inhalation	2 survived, hospitalized for 13 and 27 days
Walton	Accident	Inhalation	1 died, 6 survived
Sobonya	Accident – Explosion	Inhalation	Died on Day 60
Montague et al.	Accident	Inhalation	14 survived
Price et al.	Accident – Gas Leak	Inhalation	Died on Day 85
Darchy et al.	Accident	Inhalation	Died on Day 5
Dilli et al.	Abuse	Inhalation	Discharged Day 5

Note: See Appendix B for full reference citations.

MTOR Table

Table 89 is the MTOR table for NH_3 casualties. This table is derived from the Injury Profiles and RTD and DOW estimates from clinical case reports.

In the discussions below, which explain the other parts of Table 89, the potential for administrative declaration of asymptomatic "casualties" or delay of RTD for additional monitoring is ignored, consistent with the limitation discussed in Section 0.

Table 89. NH_3 Medical Treatment Outcome Reporting

Injury Profile	DOW[a]	CONV[a]	RTD[a]
NH_3 Mild	0%	0%	Day 2: 100%
NH_3 Moderate	0%	0%	Day 3: 100%
NH_3 Severe	0%	0%	Day 8: 100%
NH_3 Very Severe	Day 31: 27%	Day 15: 36% Day 29: 37%	Day 91: 73%

[a] Reported values indicate the fraction that changes status on a given day; they are not cumulative.

Based solely on the Injury Profiles, casualties in the NH_3 Mild cohort will recover sufficiently to RTD on Day 1, so they are reported as RTD on Day 2 in the MTOR.

Individuals in the Moderate cohort will take longer to recover. Two of the clinical case reports listed in Table 88 describe patients whose symptoms fit with the moderate cohort that were given medical treatment. Walton describes an individual who had a light exposure to NH_3 that resulted in a burn on the left eye. The patient was treated with oxygen

and eye wash and returned to work 3 days after exposure.[317] The second report describes five men who were exposed and experienced chest pain, cough, and dyspnea and were all discharged from the hospital on the second day.[318] Similarly, Caplin reports that most patients (24/27) in his "moderate" group were discharged between 10 and 30 hours after admission; recall, however, that Caplin also commented that because of the frequency of air raids in London at that time, patients were discharged earlier than they might otherwise have been,[319] so it seems reasonable to think that his patients would have remained until sometime during the second day if not for the need to keep beds available. These reports indicate a slightly more rapid recovery than that indicated in the Injury Profile—recovery some time on the second day, instead of at the end of Day 3. Thus, casualties in the NH_3 Moderate cohort are reported as RTD on Day 3, based on an expected recovery time of sometime within 2 days and following the *AMedP-7.5* reporting rules from Table 15.

NH_3-exposed individuals in the Severe cohort will take longer to recover, but with supportive care, the recovery time will likely be shortened relative to the Injury Profile. Montague et al. describe nine patients with "abnormal chest findings manifested as rales, rhonchi, and wheezing" who were hospitalized for a mean duration of 6.3 days.[320] Caplin states that the four patients in his "severe" group that survived were discharged from the hospital after 9 days.[321] A weighted average of these data points ({9 patients, 6.3 days}, {4 patients, 9 days}) yields an estimate of 7.13 days. Based on an expected recovery time of 7.13 days and following the *AMedP-7.5* reporting rules from Table 15, casualties in the NH_3 Severe cohort are reported as RTD on Day 8.

Since there is no PF_{MT} estimate for NH_3 (see Subsection 0), the Very Severe Injury Profile is not split into multiple subgroups, and there is no change in the concentration-times to which it applies. Table 88 lists 8 reports covering a combined 22 cases that would have been lethal without medical treatment, of which only 6 ended in death. Based on these clinical case reports, the model estimates the efficacy of medical treatment by reducing the lethality rate for individuals in this cohort to 27% (~6/27). For casualties who die when given medical treatment, their time until death is prolonged with treatment. The stated durations in the reports ranged between 6 hours and 85 days. Thirty days was arbitrarily chosen as the time until death with treatment and is reported in the MTOR as DOW on Day 31.

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317 M. Walton, "Industrial Ammonia Gassing," *British Journal of Industrial Medicine* 30, no. 1 (January 1973): 81.

318 Terrance J. Montague and Arthur R. Macneil, "Mass Ammonia Inhalation," *Chest* 77, no. 4 (April 1980): 496.

319 Caplin, "Ammonia-Gas Poisoning Forty-Seven Cases," 95–96.

320 Montague and Macneil, "Mass Ammonia Inhalation," 496.

321 Caplin, "Ammonia-Gas Poisoning Forty-Seven Cases," 96.

Of the 16 cases we found in the literature of survival despite symptoms compatible with *AMedP-7.5*'s "Very Severe" Injury Profile, only 11 were reported with information about the duration of recovery. The duration was either described as the length of time spent in the hospital or the time until the individuals returned to work. In *AMedP-7.5,* the hospital discharge time is the estimate of when casualties become CONV, and the time that an individual can return to work is the estimate of when casualties become RTD. The clinical reports provide a range of the hospital discharge time to be between 13 and 27 days. To represent this range of hospitalization time without making an overly detailed model, we arbitrarily split the 73% modeled to survive between 14 and 28 days (weighted heavier at 28 days to match the data). The first and second groups of CONV are reported on Day 15 and Day 29, respectively, in the MTOR. Five cases reported the time that the individuals returned to work after recovery, and it ranged between 6 weeks and 6 months. To simplify the model, all survivors who are medically treated in the Very Severe cohort are modeled to RTD at 3 months and are reported in the MTOR as RTD on Day 91. To be clear: all survivors first become CONV and then later become RTD.

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1.11. AC Model (*AMedP-7.5 Section 4.2.11*)

Introduction

Hydrogen cyanide (AC) is a "blood" or systemic chemical agent that was used during WWI[322] and is now often referred to as a TIC because of its use in the chemical industry;[323] however, we refer to it as a chemical agent. AC's primary mechanism of injury is preventing cellular respiration.

The objective of this chapter is to describe the human response model for AC as it has been incorporated into *AMedP-7.5*. The chapter first discusses assumptions for the scope. Then it describes the physiological effects of AC, the toxicity parameters used in *AMedP-7.5*, development of Injury Profiles, and the medical treatment model.

Assumption (*AMedP-7.5 Section 4.2.11.2*)

> **Assumption**: Percutaneous exposure to AC vapour and liquid are negligible.

The percutaneous vapor is assumed negligible because in all the research performed in the development of this model, no sources were found that discussed AC injury resulting from percutaneous vapor exposure. Further, the liquid resulting from an AC attack, and thus the percutaneous liquid contribution to dose, may be neglected due to the agent's high volatility. Finally, FM 3-11.9 lists the skin and eye toxicity as "none" for AC.[324] This assumption may result in an underestimate of the number and severity of casualties.

Physiological Effects[325] (*AMedP-7.5 Table 4-37*)

> **Note:** While there are several toxic cyanide compounds, exposure to cyanide in any form will result in a common set of symptoms. The specific chemistry of the parent compound, however, may cause additional effects specific to that compound. Where appropriate in this document, "cyanide" is used to refer to general effects, and the compound abbreviation (e.g., AC or CK) is used to refer to compound-specific effects.

Cyanide affects the body by inhibiting some 40 enzymes, but its dominant effects result from its inhibition of cytochrome *c* oxidase, the terminal protein in the electron-transport chain, which prevents the transfer of electrons to molecular oxygen. Thus, despite its presence in the blood, the body cannot use oxygen for adenosine triphosphate

322 Tuorinsky and Sciuto, "Toxic Inhalational Injury," 342 (Table 10-2).

323 Ibid., 343 (Table 10-3).

324 USACMLS, *Chemical/Biological Agents and Compounds*, III-32.

325 This section is mostly paraphrased from Steven I. Baskin et al., "Cyanide Poisoning," chap. 11 in *Medical Aspects of Chemical Warfare*, ed. Shirley D. Tuorinsky, Textbooks of Military Medicine (Washington, DC: Office of the Surgeon General, Borden Institute, Walter Reed Army Medical Center, 2008); Hurst et al., *Medical Management of Chemical Casualties*.

generation, and aerobic cell metabolism ceases. This systemic condition, histotoxic anoxia or progressive tissue hypoxia, manifests in different ways depending on the degree of exposure.

At any inhaled dosage, the first observable effect is a transient increase in the rate and depth of breathing, followed by shortness of breath and slower breathing. Other low-dosage symptoms may include excitement, anxiety, dizziness, headache, muscle weakness, and nausea. For an intermediate dosage, the shortness of breath worsens, and vomiting, drowsiness, and muscle spasms can occur in addition to the lower dosage exposure symptoms. With any dosage that does not incapacitate the individual, removal from exposure is sufficient to ensure that symptoms will not worsen and medical treatment is likely unnecessary. The body recovers quickly from small amounts of cyanide because of natural detoxification; however, natural recovery mechanisms can be swamped by large amounts of cyanide.

With high dosage, respiration still increases temporarily but shortly becomes slow and gasping, and the victim may become apneic. Unconsciousness and convulsions occur within minutes. Because victims are incapacitated so quickly, they often cannot remove themselves from exposure or don protective equipment. If removed from exposure promptly, an unconscious person may or may not spontaneously recover, depending on the total dosage received. The effect of medical treatment on the prognosis for victims of AC exposure is discussed in Section 0. With or without medical treatment, cyanide casualties may develop long-term neurological sequelae, but because no specific data on the rate of occurrence or time of onset are available, the models do not include sequelae.

Table 90 summarizes the preceding qualitative descriptions in a format amenable to use in *AMedP-7.5* and for the analysis presented in this chapter. Consistent with the definition of Injury Profile, the symptom sets are clinically differentiable. The next part of the model derivation is to define four sets of toxicity parameters, each associated with a *peak* Injury Severity Level equal to one of the four levels defined in Table 90.

Table 90. Association of AC Injury Severity Levels with AC Symptom Sets

Injury Severity Level	Set of Symptoms
0	No observable injury
1 (mild)	Nausea; fatigue and weakness; transient rapid breathing followed by slower breathing; shortness of breath; excitement; anxiety; dizziness; headache
2 (moderate)	Episodes of vomiting; increased fatigue and weakness; muscle spasms; difficult to breathe; drowsiness
3 (severe)	Severe generalized twitching with or without convulsions; breathing sporadically stops and starts; unconsciousness
4 (very severe)	Convulsions; breathing stops completely; coma

Toxicity Parameters (*AMedP-7.5 Table 4-37*)

The CSAC report on AC is FOUO, so it was not used. ECBC-TR-856 reports the LCt_{50}, $ECt_{50\text{-severe}}$, and probit slope for both levels of effect to be 600 mg-min/m^3, 1400 mg-min/m^3, and 12.0 probits/log (dose).[326] ECBC-TR-856 provides the most trustworthy toxicity estimates among sources that could be used in a NATO document without a "NATO UNCLASSIFIED" or higher marking.[327]

The remaining question is, what values should be used for the moderate and mild effect levels? Since the primary mechanism of cyanide toxicity (cytochrome *c* oxidase inhibition) does not vary by severity of injury, we assumed that the mild, moderate, and severe probit slopes are equal to the lethal probit slope.[328] This assumption also helps avoid illogical results such as two toxicity curves intersecting. For all levels of effect, we use 12.0 probits/log (dose) as the estimated probit slope.

Our literature review, including the AEGL document for AC,[329] identified only five cases of human exposure that can be used for estimating median toxicities for mild and moderate effects. Table 91 summarizes the human data that we deemed usable for this purpose. Where ranges are reported, either multiple people were involved, or a range of concentrations was given in the original report. In the last row, the value is approximate because the time of exposure is reported as approximately 1 minute.

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326 Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*, 26.

327 See the following report for information on alternate toxicity estimate sources: Oxford et al., *Parameters for Estimation of Casualties*, 64–65.

328 This principle is applied for several agents in Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*.

329 National Research Council, "Hydrogen Cyanide: Acute Exposure Guideline Levels," vol. 2 of *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (Washington, DC: The National Academies Press, 2002).

Table 91. Relevant Non-Lethal Human Inhalation Exposures to AC

Source	Inhaled Dosage (mg-min/m^3)	Exposure Duration (min)[a]	Symptoms	Apparent Injury Severity Level
Bonsall	1500	3.0	Unconsciousness	3
Barcroft	820–1030	1.5	Nausea, difficulty concentrating	1
Grubbs	550–620	1.5 – 2.0	None or dizziness	1
Katz	550–575	1.0	None	0
Bonsall	~500	~1	Dizziness, confusion	1

Note: See Appendix B for full reference citations.

[a] This is the duration before the onset of symptoms; in some cases, exposure continued for a longer time.

Since the Table 91 data are sparse, we turned to animal data. In reviewing the literature, we found that the primary focus of AC inhalation animal studies in historical research has unfortunately been lethality. Further, in reports focused on lethality testing, the symptoms of the animals are generally not described. The only information typically reported other than dosage-related information is the number of animals tested and the number that died. A few reports do indicate that animals survived their exposure even after being rendered unconscious, but since they were unconscious, the data are not relevant for estimating moderate and mild toxicity parameters.[330] Sommerville et al. used these types of data to develop their estimate of the $ECt_{50\text{-severe}}$. The relatively small pool of data relevant for mild and moderate toxicity parameters resulted in the need to use suboptimal data, as described below.

Table 5-5 of the AEGL report for AC[331] summarizes a separate set of sublethal inhalation data from laboratory animals. Based on the National Research Council (NRC) literature review and our own review, these data appear to be the only available examples of sublethal animal exposoure. Most of the data are from rodents, but a few data points are from monkeys. To minimize issues related to different species sensitivity,[332] we chose to use the monkey data and the human data listed in Table 91 to develop our mild and moderate ECt_{50} estimates.

330 Some of these data were, however, useful for developing Injury Profiles—see Section 0.

331 National Research Council, “Hydrogen Cyanide.”

332 The fact of sensitivity differences and the difficulties of dealing with different species of laboratory animals are well documented: Barcroft, “The Toxicity of Atmospheres”; B. P. McNamara, *Estimates of Toxicity of Hydrocyanic Acid Vapors in Man*, EB-TR-76023 (Aberdeen Proving Ground, MD: Headquarters, Edgewood Arsenal, August 1976), ADA028501; Sommerville et al., *Review and Assessment of Hydrogen Cyanide*; National Research Council, “Hydrogen Cyanide.”

The monkey data come from three separate reports. We were unable to acquire the first, by Dudley, Sweeney, and Miller,[333] and can therefore only use the information reported in the Table 5-5 of the AC AEGL document: exposure to 137.5 mg/m^3 for 12 minutes was "distinctly toxic" to monkeys (species not stated). But as we will see below, the minute volume (and changes thereof during the exposure) plays a critical role, so this data point could not be used with the others.

The second report[334] and third report[335] describe experiments that involved challenging cynomolgus macaques (CMs) weighing between 3 and 4 kg to AC via a face mask (other gases and mixtures were also tested, but those data are not of interest here). In the first article, it is reported that CMs exposed to 66 mg/m^3 for up to 30 minutes showed no symptoms, and changes in measurable signs like minute volume were minimal. The second article also synopsizes the results reported in the third: at higher concentrations, the CMs would hyperventilate and then become semiconscious—defined as loss of muscle tone and reflexes but able to be awakened briefly if touched—with slow deep breaths and a pause at the end of each breath. The report also states that hyperventilation began within 30 seconds of the start of exposure. Based on the descriptions in Table 90, the onset of hyperventilation matches mild symptoms, and the onset of "semiconsciousness" matches moderate symptoms.

Purser, Grimshaw, and Berril reported AC challenge concentrations (single values given—no time dependence was reported) and the time to semiconsciousness. They also commented on the time at which two CMs began showing symptoms that match the severe description in Table 90 (cessation of breathing or convulsions). The concentration- and symptom-related data are shown in Table 92. Finally, they provided a plot of minute volume as a function of time for *one* of the CMs, reproduced as Figure 4. We digitally extracted the minute volume data from their figure at 30-second intervals (see Table 93).

The following analysis involves a number of assumptions and far from ideal strategies for using the CM data. Although our general preference is to base our models on more rigorous methods, the poor quality of the data available left us with no other choice. Thus, although we propose values for the $ECt_{50\text{-mild}}$ and $ECt_{50\text{-moderate}}$ at the end of this section, we

333 H. C. Dudley, T. R. Sweeney, and J. W. Miller, "Toxicology of Acrylonitrile (Vinyl Cyanide). II. Studies of Effects of Daily Inhalation," *Journal of Industrial Hygiene and Toxicology* 24 (1942): 255–258.

334 David A. Purser, "A Bioassay Model for Testing the Incapacitating Effects of Exposure to Combustion Product Atmospheres Using Cynomolgus Monkeys," *Journal of Fire Sciences* 2, no. 1 (1984): 20–36.

335 David A. Purser, Patricia Grimshaw, and Keith R. Berril, "Intoxication by Cyanide in Fires: A Study in Monkeys Using Polyacrylonitrile," *Archives of Environmental Health* 39, no. 6 (1984): 394–400.

recognize the high degree of uncertainty associated with them and recommend that when possible, new values be generated based on stronger datasets.

Table 92. CM Dose-Response Data Reported by Purser, Grimshaw, and Berril

Experiment No.	Hydrogen Cyanide (AC) Concentration (mg/m^3)	Time to Semiconsciousness (min)	Time to Convulsions (min)
E15	171.6	8	Not reported
E16	112.2	16	Not reported
E19	161.7	8	27
E20	135.3	15	28
E21	110.0	19	Not reported

Note: The report also states that hyperventilation began within 30 seconds of the start of exposure. We assumed that this condition applies to all five cases.

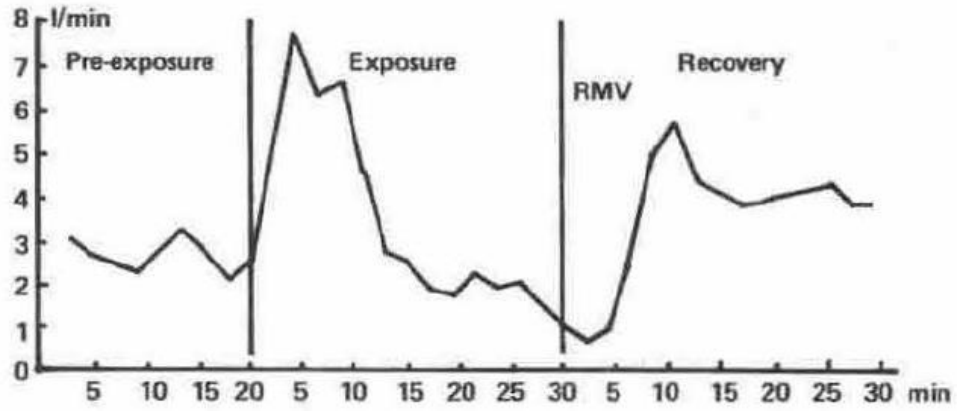

Figure 4. CM Minute Volume Data Reported by Purser, Grimshaw, and Berril

Table 93. CM Minute Volume Data Extracted from Figure 4

Time (min)	Minute Volume (L/min)	Time (min)	Minute Volume (L/min)	Time (min)	Minute Volume (L/min)
0.0	2.46	7.0	6.34	14.0	2.58
0.5	2.92	7.5	6.42	14.5	2.53
1.0	3.61	8.0	6.47	15.0	2.45
1.5	4.29	8.5	6.54	15.5	2.32
2.0	4.92	9.0	6.36	16.0	2.19
2.5	5.55	9.5	5.82	16.5	2.05
3.0	6.17	10.0	5.30	17.0	1.91
3.5	6.83	10.5	4.84	17.5	1.81
4.0	7.57	11.0	4.48	18.0	1.79
4.5	7.50	11.5	4.08	18.5	1.75
5.0	7.21	12.0	3.64	19.0	1.73

Time (min)	Minute Volume (L/min)	Time (min)	Minute Volume (L/min)	Time (min)	Minute Volume (L/min)
5.5	6.87	12.5	3.19	19.5	1.71
6.0	6.58	13.0	2.69	20.0	1.82
6.5	6.27	13.5	2.63		

Using the EPD formula given in Eq. 4, we first calculated each CM's EPD at half-minute intervals (using a constant concentration over time since no more detailed information was provided). Next, we used the minute volume data in Table 93 to estimate the cumulative EPD-adjusted *dose* (in units of milligrams) for each CM as a function of time, using the TLE recommended for *humans*[336] by ECBC-TR-856 ($n = 2$).[337]. Finally, we scaled each CM's cumulative EPD-adjusted dose over time to an estimated equivalent human EPD over time. The final step required the use of a human mass, a CM mass, and a human minute volume. The human mass used was 70 kg, and to handle the uncertainty related to the reported CM masses, the final step was done twice: once using 3 kg CM mass and once using 4 kg CM mass.

The human minute volume used was based on the measured CM minute volume. Not accounting for the changes in the CM minute volume would significantly alter the result, given that the minute volume dramatically changed during the exposures. The "standard" human minute volume of 15 L/min was multiplied by the ratio of the average CM minute volume (from the beginning of the challenge up to the time point being estimated) to the average pre-exposure CM minute volume (calculated from data extracted from Figure 4—average pre-exposure minute volume was 2.64 L/min).

Having the estimated human EPDs, we then checked what the values were at the times Purser, Grimshaw, and Berril reported for the onset of moderate or severe symptoms. Since the reported time to hyperventilation was only 30 seconds, the previous process, minus the EPD calculations, was used to estimate an equivalent human dosage for hyperventilation. Table 94 reports the results with EPD and dosage estimates rounded to the nearest one. The results for the moderate and severe effects are only reported for 4 kg results because they are clearly inconsistent with the lethal and severe level toxicity estimates from Sommerville et al. For example, the Table 94 results indicate the onset of moderate symptoms at EPD around 1800–2200 mg-min/m^3, whereas the $ECt_{50\text{-severe}}$ reported by ECBC-TR-856 is 1400 mg-min/m^3, and the 3 kg results are even more inconsistent (the estimated EPDs are higher). Further, the estimated human equivalent dosages for

336 Since the purpose of the analysis described here is to eventually extrapolate from CMs to humans, the underlying assumption in applying the human TLE to CMs seems acceptable. At worst, it is no worse than the other assumptions required to make use of the CM data.

337 Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*, 26.

hyperventilation are low, relative to the data reported in the second through fifth rows of Table 91. Thus, it seems this approach is not fruitful.

Table 94. Estimated Human EPDs as Compared to Symptoms Observed in CMs, with Assumed CM Mass 4 kg

	Estimated Human EPD or Dosage (mg-min/m^3) Based on ...				
Symptom	**E15**	**E16**	**E19**	**E20**	**E21**
Hyperventilation	265	173	250	209	170
Semiconsciousness	1868	1946	1761	2178	2138
Cessation of breathing or convulsions		4143	3564		

Note: The letter "E" followed by a number indicates an Experiment Number (e.g., E15 = Experiment Number 15).

The preceding results were not entirely unexpected, since there are unknown differences in species sensitivity between humans and CMs. This approach might seem to contradict the choice of CM data instead of rodent data, except that the CM data can be used to estimate the *ratio* of $ECt_{50\text{-moderate}}$ to $ECt_{50\text{-severe}}$ (the value of the latter being taken from Sommerville et al.).[338] Thus, there is still value in using CMs instead of rodents since it is reasonable to expect that the ratio for CMs and humans will be more similar than the ratio for rodents and humans.

To estimate the ratio, the process of extrapolating to human mass and minute volume (which adds a layer of uncertainty) is not needed. Thus, the EPD-adjusted *dose* (in units of milligrams) for each CM, as a function of time, was used. These values account for toxic load effects using the estimated *human* TLE and the reported minute volume for one monkey. Table 95 contains the calculated doses corresponding to the symptoms of interest. Table 96 contains calculated ECt_{50} ratios, based on equating semiconsciousness to moderate and cessation of breathing or convulsions to severe.

Table 95. Estimated CM EPD-Adjusted Dose for Different Endpoints

	Estimated CM EPD-Adjusted Dose (mg) Based on ...					
Symptom	**E15**	**E16**	**E19**	**E20**	**E21**	**Average**
Semiconsciousness	3.49	3.05	3.29	3.59	3.08	3.30
Cessation of breathing or convulsions			4.92	4.14		4.53

Note: The letter "E" followed by a number indicates an Experiment Number (e.g., E15 = Experiment Number 15).

338 Attempting a similar exercise for estimating the $ECt_{50\text{-mild}}$ again produced results that are very low relative to the available human data, so the results of that exercise are not shown here.

Table 96. Estimated $ECt_{50\text{-moderate}}/ECt_{50\text{-severe}}$ for CMs, Based on Table 95 Data

ECt_{50} Ratio	Ratio
Based on averages	0.73
Based on E19 and E20	0.77

If the ECt_{50} ratios for CMs are applied to humans, the Table 96 values and ECBC-TR-856's $ECt_{50\text{-severe}}$ estimate of 1400 mg-min/m^3 indicate that $ECt_{50\text{-moderate}}$ is either 1022 or 1078 mg-min/m^3. Given the high uncertainty of this entire analysis, we chose to simply round the estimate off at 1100 mg-min/m^3. Given the probit slope of 12.0, the approximate range for of the moderate toxicity curve (ECt_{10} to ECt_{90}) is 860 to 1400 mg-min/m^3.

We can now do a consistency check with the few pieces of human data available (summarized in Table 91).[339] The first row (Bonsall) reports a dosage of 1500 mg-min/m^3 and severe symptoms, which is not inconsistent with an $ECt_{90\text{-moderate}}$ of 1400 mg-min/m^3 or the ECBC-TR-856 $ECt_{10\text{-severe}}$ of 1100 mg-min/m^3. The other four dosages listed in Table 91 led to mild or no symptoms, and they are either at the low end of the moderate curve or far below the moderate curve, which is also consistent.

We still do not have an $ECt_{50\text{-mild}}$ estimate, and there seem to be no suitable data for estimating it other than the Table 91 data. Barcroft quotes Katz and Longfellow: "in experiments during the war, men have been exposed to [550 mg/m^3] for about a minute without injury."[340] The statement seems to be based on multiple experiments, indicating that 550 mg/m^3 should be near the bottom of the mild toxicity curve. This finding is consistent with the report by Grubbs that several volunteers inhaled dosages of about 550 to 620 mg-min/m^3 over 1.5 to 2 minutes and felt no effect, but "this has at other times caused dizziness."[341] Causing dizziness in some cases, but more often causing no symptoms (as seems to be implied from Grubbs' wording), is consistent with the bottom of a toxicity curve. On the other hand, Bonsall reported that a man exposed for around a minute to a 500 mg/m^3 atmosphere felt dizzy and confused, so 500 mg-min/m^3 should not be *too* low on or entirely off the toxicity curve. Barcroft's self-exposure experiment, in which his dosage was between 820 and 1030 mg-min/m^3, clearly caused mild symptoms. None of this information provides an obvious answer for the $ECt_{50\text{-mild}}$ estimate, so we simply picked a value that reasonably aligns with the human data from Table 91, which are

339 Note that given the short durations of the exposures reported, no EPD calculations are warranted.

340 Joseph Barcroft, "The Toxicity of Atmospheres Containing Hydrocyanic Acid Gas," *The Journal of Hygiene* 31, no. 1 (1931): 25. We were unable to acquire the Katz and Longfellow report.

341 S. B. Grubbs, "Detection of Hydrocyanic Acid Gas: Use of Small Animals for This Purpose," *Public Health Reports* 32, no. 16 (1917): 566.

summarized in this paragraph. An $ECt_{50\text{-mild}}$ of 700 mg-min/m^3 gives a toxicity curve with an approximate range (ECt_{10} to ECt_{90}) of 550 to 900 mg-min/m^3.

Although the human data cannot be said to *validate* the $ECt_{50\text{-moderate}}$ estimate derived from the CM data, the data are consistent with the estimate. The $ECt_{50\text{-mild}}$ estimate is based directly on human data, but it can only be said that the value is generally consistent with the data, not that it is *derived* (in a mathematical sense) from the data. Given the lack of other data suitable for generating estimates of these parameters, we used them for our models. The final set of median toxicities and probit slopes for inhaled AC is summarized in Table 97. To repeat some previous caveats: there is high uncertainty surrounding the mild and moderate ECt_{50}s, due to the number of assumptions required in the analysis, but given the poor quality of the data, these are the best estimates available. When possible, however, new values based on better supporting data should be derived and used in *AMedP-7.5* (or perhaps its successor).

Table 97. Median Toxicities and Probit Slopes for Inhaled AC

Injury Profile	Effect	Median Toxicity[a] (mg-min/m^3)	Probit Slope (Probits/Log (dose))
AC Very Severe	Lethal	2600	12.0
AC Severe	Severe	1400	12.0
AC Moderate	Moderate	1100	12.0
AC Mild	Mild	700	12.0

[a] The median toxicity is an estimate for a 2-minute exposure.

Injury Profiles (*AMedP-7.5 Table 4-38*)

Cyanide is far less toxic than GB and VX, so its military relevance hinges on its quick action. At sufficient concentration, it can incapacitate within 15 seconds.[342] Since *AMedP-7.5* defines time zero in its human response models as the time at which exposure ends, Injury Profiles for AC begin at the maximum Injury Severity Level they will reach.

The next several paragraphs describe the information used to determine the progression of cyanide injury in the absence of medical treatment. The open literature contains many clinical case reports describing symptoms and recovery after exposure to a cyanide, typically by ingestion of a cyanide salt, but most of these reports are not applicable here because medical treatment was provided. They are considered in Section 0. Because most human data can only be used for the medical treatment models, we were left with very little data on which to base the Injury Profiles. For that reason, we also used some

342 George H. Mangun and John W. Perry, *A Study of the Comparative Toxicity of HCN to Man and Animals*, TDMR 430 (APG, MD: Chemical Corps Technical Command, Army Chemical Center, 27 August 1942), 6; George H. Mangun and Howard B. Skipper, *Hydrocyanic Acid. The Speed of Action on Man*, TDMR 471 (APG, MD: Chemical and Radiological Labs, Army Chemical Center, 17 November 1942), 3.

animal data either to derive parts of Injury Profiles or to check for consistency the parts of a profile that are based on a small pool of human data or low-quality human data.

The only sources describing specific incidents of cyanide injury in humans consistent with the mild symptoms listed in Table 90 are summarized in the bottom four rows in Table 91. Of these, only Barcroft's description of a "momentary feeling of nausea"[343] gives some estimate of the duration of symptoms. In contrast to his description, later reports[344] on Barcroft's experiment state that some of his symptoms persisted for about a year, so it seems that Barcroft's response was atypical. While this section of the document is not concerned with RTD estimates per se, such estimates do give upper bounds for recovery time. The *MMCC* says, "those with mild to moderate effects from the agent can usually return to duty within hours."[345] Similarly, a U.K. military source states that "in mild cases there may be headache, vertigo, and nausea for several hours before complete recovery."[346] These statements are consistent with the observations of Purser, Grimshaw, and Berril related to the CM experiments used to derive toxicity parameters. The report states that "the animals appeared to be perfectly normal within a few hours."[347] Since no more specific data are available, general statements were used for the model, and the AC Mild Injury Profile therefore decreases from Injury Severity Level 1 to Injury Severity Level 0 at 2 hours, as shown in Table 98. The choice of 2 hours, instead of some other number that could be meant by "several" or "few" is arbitrary. But since the reporting resolution of *AMedP-7.5* is 1 day, the specific value has little effect. Recovery definitely occurs in less than 1 day and will be modeled as such in *AMedP-7.5*.

We found no human data that could be used for the AC Moderate Injury Profile, and the only animal data was again from Purser, Grimshaw, and Berril, whose description of the "semiconscious" state of the CMs aligns best with the moderate symptoms in Table 90. Their report states that the animals recovered from the semiconscious state to a "fairly active state"[348] within 10 minutes of the end of exposure, and that full recovery occurred within a few hours. These statements are implemented as a decrease from Injury Severity Level 2 to Injury Severity Level 1 at 10 minutes, and a further decrease to Injury Severity Level 0 at 3 hours, as shown in Table 98. As before, 3 hours is arbitrary. We chose 2 hours for Mild and 3 hours for Moderate because we take "a few" to mean 2 to 3 (hours) and recovery from Moderate should be slower than recovery from Mild symptoms. The AC

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343 Barcroft, "The Toxicity of Atmospheres," 25.

344 McNamara, Estimates of Toxicity, 13; R. Macy, *Hydrocyanic Acid: Its Military History and a Summary of Its Properties*, EATR 219 (APG, MD: Edgewood Arsenal, 20 May 1935), 6.

345 Hurst et al., *Field Management of Chemical Casualties*, 61.

346 Royal Army, "Cyanogen Agents," *Journal of the Royal Army Medical Corps* 148, no. 4 (2002): 384.

347 Purser, Grimshaw, and Berril, "Intoxication by Cyanide in Fires," 397.

348 Ibid., 399.

Moderate Injury Profile is consistent with the two military sources cited in the previous paragraph, and we note again that since the reporting resolution of *AMedP-7.5* is 1 day, the specific value has little effect. Recovery definitely occurs in less than 1 day.

For the AC Severe Injury Profile, we located a single one-page report that summarizes the symptoms of five men who were rendered unconscious by exposure to AC.[349] For three of the men, the incident is described. A valve leak allowed AC to escape, and nine men were exposed. The three who lost consciousness were moved out of the area by those who did not lose consciousness.[350] For the other two men, the circumstances of the exposure are not reported (the incidents were different from the leaking valve that exposed the other nine), but they were also presumably moved from the area of exposure by coworkers. No dosage estimate is reported for any of the exposed. Peden et al. stated that in all five cases of unconsciousness, "their conscious level had largely returned even in the short time before the arrival of the works medical officer (probably less than 10 minutes)."[351] Although the men were attended to by a medical officer, they did not receive any antidotes (only oxygen), so their symptom progression after the arrival of the medical officer is relevant. The report states that four of the nine exposed in the leaking valve incident had a headache that persisted for up to 8 hours. Although the report does not specify which four men, we assume that three of them were those that had been unconscious.

We also found some comments on animal recovery from experiments in which "lethal" doses were given. Trautman conducted antidote testing with guinea pigs, rats, and rabbits and also reported on the control animals. The experiment involved placing the animal in an AC environment "until it was thought that it had breathed in a near-lethal, or lethal, dose of the HCN gas,"[352] which we presume to indicate that animals were unconscious before being removed from the challenge environment. He defined "recovery" as "when the animal had regained the use of its legs and was able to move forward."[353] We would define Trautman's "recovery" as a decrease from Injury Severity Level 3 to Injury Severity Level 2 since it seems based on the animal's regaining consciousness. He noted that control animals that survived "recovered" in about 13 minutes, consistent with the Peden et al. human data. Armstrong reported on similar experiments with mice, stating that

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[349] N. R. Peden et al., "Industrial Exposure to Hydrogen Cyanide: Implications for Treatment," *British Medical Journal* 293, no. 6546 (1986): 538.

[350] Unfortunately, Peden et al.'s report does not give any information about the men who did not lose consciousness that could be used for the Mild or Moderate AC Injury Profiles.

[351] Peden et al., "Industrial Exposure to Hydrogen Cyanide."

[352] J. A. Trautman, "Methylene Blue in the Treatment of HCN Gas Poisoning," *Public Health Reports* 48, no. 48 (1933): 1445.

[353] Ibid.

survivors regained consciousness within 5–10 minutes.[354] As for recovery beyond simply regaining consciousness, we could only find one report that gave any statement related to the timing (many reports mention that animals survive but do not state recovery timelines). Silver, McGrath, and Krackow reported that goats that had been exposed sufficiently to cause convulsions "recovered completely in several hours."[355]

Taking these human and animal data together, with the animal data mainly serving as confirmation that Peden et al.'s observations were not abnormal, we decided to model recovery from Injury Severity Level 3 to 2 at 10 minutes. Based on Peden et al.'s observation of headaches persisting up to 8 hours, we also decided to model full recovery (to Injury Severity Level 0) at 8 hours. Since there is no specific information related to the step from Injury Severity Level 2 to Injury Severity Level 1, we model it as one-quarter of the time until full recovery, based on the vague sense of the recovery from the more severe symptoms happening relatively more rapidly than full recovery. *MMCC* says only that "those successfully treated after severe effects can return [to duty] within a day,"[356] which is consistent with the proposed model, even though it refers to the case *with treatment*. Note that Section 1.B.7.a also shows that these estimates are consistent with other human data for cases in which medical treatment was given. Table 98 shows the complete AC Severe Injury Profile. Recognizing the arbitrariness of the exact times used, we again remind the reader that since *AMedP-7.5* uses 1-day time resolution, the fact that recovery occurs within a day is what is most important.

For the AC Very Severe Injury Profile, three reports by men who witnessed executions by AC inhalation provide evidence that death occurs between 6 and 13 minutes.[357] This finding is consistent with the *AMedP-7.5* value of the parameter $T_{death\text{-}CN\text{-}SL4}$, 15 minutes, so the AC Very Severe Injury Profile ends at 15 minutes.

Table 98 summarizes the AC Injury Profiles described in this section.

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354 G. C. Armstrong, *Toxicity of Hydrocyanic Acid Gas to Mice by Inhalation for a 10-Min Exposure*, EATR 136 (Edgewood Arsenal, MD: Chemical Warfare Service, 1933), 6, ADB956969.

355 S. D. Silver, F. P. McGrath, and E. H. Krackow, *Hydrocyanic Acid LC50 for Goats: 2 Min Exposure Time for Incapacitation*, TRLR 23 (Washington, DC: Chemical Warfare Service, 07 January 1944), 4, ADB967768.

356 Hurst et al., *Medical Management of Chemical Casualties*, 61.

357 Mangun and Perry, *A Study of the Comparative Toxicity of HCN*; Mangun and Skipper, *Hydrocyanic Acid*; Jack Wexler, James L. Whittenberger, and Paul R. Dumke, "The Effect of Cyanide on the Electrocardiogram of Man," *American Heart Journal* 32, no. 2 (1947): Figures 5–7.

Table 98. Inhaled AC Injury Profiles

Time Point (min)	AC Mild	AC Moderate	AC Severe	AC Very Severe
1	1	2	3	4
10	1	1	2	4
15	1	1	2	4[a]
120	0	1	1	
180	0	0	1	
480	0	0	0	

[a] Death is modeled to occur at this point, based on the default value of the parameter $T_{death\text{-}CN\text{-}SL4}$ in *AMedP-7.5*.

Medical Treatment (*AMedP-7.5 Table 4-39*)

7. Efficacy of Medical Treatment

Medical treatment of cyanide poisoning involves supportive care and administration of antidotes[358] that can rapidly reactivate the enzymes deactivated by cyanide. Supportive care alone is sometimes able to sustain life until complete recovery, but antidotes speed the process by assisting the body's natural cyanide detoxification mechanisms. Several clinical antidotes and other compounds have been tested for pre- and post-exposure prophylactic efficacy,[359] but since none are currently in use as prophylactics, the models do not include prophylaxis.

No self-aid or buddy aid is available for battlefield administration of cyanide antidotes. A Role 1 MTF or its equivalent is the nearest location at which a soldier could receive cyanide antidote therapy. The specific antidote used varies by country. There is no widespread agreement on the relative efficacies of different antidotes, but some studies indicate little difference.[360] There are differences in the safety profiles, but it is reasonable

358 If available. As discussed below, antidotal therapy is only available at MTFs.

359 James L. Way, Stanley L. Gibbon, and Maureen Sheehy, "Cyanide Intoxication: Protection with Oxygen," *Science* 152, no. 3719 (1966): 210–211; James L. Way, Stanley L. Gibbon, and Maureen Sheehy, "Effect of Oxygen on Cyanide Intoxication I. Prophylactic Protection," *Journal of Pharmacology and Experimental Therapeutics* 153, no. 2 (1966): 381–385; Arthur S. Hume, *Study of Potential Prophylactic and Antidotal Use of Scavenging Agents in Treatment of Cyanide Poisoning* (Jackson, MS: Department of Pharmacology and Toxicology, University of Mississippi Medical Center, 15 November 1984). ADB122469.

360 Charles L. Rose et al., "Cobalt Salts in Acute Cyanide Poisoning," *Proceedings of the Society for Experimental Biology and Medicine* 120, no. 3 (1965): 780–783; G. Paulet, R. Chary, and P. Bocquet, "The Comparative Value of Sodium Nitrite and Cobalt Chelates in the Treatment of Cyanide Intoxication in Non-Anesthetized Animals," *Archives Internationales de Pharmacodynamie et de Thérapie* 127 (1969): 104–117; Alan H. Hall and Barry H. Rumack, "Hydroxycobalamin/Sodium Thiosulfate as a Cyanide Antidote," *Journal of Emergency Medicine* 5, no. 2 (1987): 115–121; Walter S. Johnson, Alan H. Hall, and Barry H. Rumack, "Cyanide Poisoning Successfully Treated without 'Therapeutic Methemoglobin Levels,'" *American Journal of Emergency Medicine* 7, no. 4 (1989): 437–440; Alan H. Hall, Richard C. Dart, and Gregory

to assume that medical personnel are trained to handle the side effects of their country's antidote regimen. The treated model includes a generic effect of medical treatment instead of considering each antidote specifically.

Literature reports on the treatment of cyanide poisoning in humans are primarily clinical case reports. In most of these reports, a person ingested potassium cyanide (KCN). In such cases, the dose cannot be directly compared to an inhaled dosage, but since the mechanism of cyanide toxicity is not dependent on the route of exposure or source of cyanide, the cases are still useful for estimating the efficacy of medical treatment. We assigned cases to Injury Profiles based on the reported symptoms. There are also reports of experiments on animal models, where a common topic is the selection of the best antidote. As noted, there is no widespread agreement. Cyanide has not been used as a chemical weapon in any recent conflicts for which data are available.

a. Human Data

Clinical case reports predominantly concern either attempted suicide, usually by ingestion of a cyanide salt, or smoke inhalation victims.[361] There are problems in using either type of report for the treated model. In ingestion cases, the actual dose is usually unknown because even if the amount ingested is known, uptake by the body before medical personnel perform gastric lavage is not known. In smoke inhalation victims, the dosage is also unknown, and the symptoms may be due to the combination of various chemicals in smoke and burn injuries. Deconvoluting the different effects is problematic.

In two cases, the total absorbed dose was known with some confidence. In the first case,[362] the patient ingested three capsules that each contained about 200 mg KCN. Because the nature of his condition was unknown to the physicians, the only treatment he received was general supportive care, without gastric lavage. In the second case, the patient, after waking up, "stated that he had accurately weighed 413 mg of pure potassium cyanide at work and taken this on an empty stomach."[363] He did receive gastric lavage but not until hours after ingestion the KCN, so it is likely he had already absorbed it all, as indicated by the physician's statement that "gastric lavage looked clear."[364]

The World Health Organization (WHO) estimated that in cases of humans ingesting cyanide poisons, the average absorbed dose of AC equivalent at the time of death was 1.4

Bogdan, "Sodium Thiosulfate or Hydroxocobalamin for the Empiric Treatment of Cyanide Poisoning?" *Annals of Emergency Medicine* 49, no. 6 (2007): 806–813.

361 Hydrogen cyanide is a common component of smoke caused by fires.

362 David L. Graham et al., "Acute Cyanide Poisoning Complicated by Lactic Acidosis and Pulmonary Edema," *Archives of Internal Medicine* 137, no.8 (1977): 1051–1055.

363 A. C. Edwards and I. D. Thomas, "Cyanide Poisoning," *The Lancet* 311, no. 8055 (1978): 92.

364 Ibid.

mg/kg.[365] The equivalent dose of KCN (in terms of moles of cyanide) is 3.6 mg/kg, or 252 mg per 70 kg man. Thus, in the two preceding cases, since it seems the entire ingested doses were absorbed, the patients survived approximately 2.4 and 1.6 lethal doses,[366] respectively. Taking the average, it appears that supportive care can save the life of a person exposed to *two* lethal doses.

The information presented above is captured in the model by the use of a protection factor. Since there is reason to believe that medical treatment that includes antidotes (PF_{SCAT}) will be even more effective than supportive care alone (PF_{SC}), we will distinguish between PF_{SC} and PF_{SCAT}, where the subscript SC indicates supportive care and the subscript SCAT indicates supportive care *plus* antidote therapy. Thus, the preceding case information, from Graham et al. and Edwards and Thomas, combined with the WHO estimate, indicates that $PF_{SC} = 2$.

Table 99 summarizes all clinical case reports that we consulted and found to be of some use for developing the treated model. None of the reports other than the two cited previously (i.e., Graham et al. and Edwards and Thomas) were suitable for estimating PF_{SCAT}, but they were used for other parts of the treated model (namely, estimating the time to RTD—see Subsection 1.B.8).

Table 99. Clinical Case Reports of Humans Exposure to Cyanide

Exposure Type	Agent	Exposure Route(s)	Source
Accident	AC	Inhalation	Chen and Rose
Accident	“Cyanide”	Inhalation	Bain and Knowles
Attempted suicide	NaCN, KCN	Ingestion	De Busk and Seidl
Accident	KCN	Ingestion, submersion	Trapp
Attempted suicide	KCN	Ingestion	Graham et al.
Attempted suicide	KCN	Ingestion	Edwards and Thomas
Attempted suicide	KCN	Ingestion	Vogel, Sultan, and Ten Eyck
Attempted suicide	KCN	Ingestion	Brivet et al.
Attempted suicide	KCN	Ingestion	Litovitz, Larkin and Myers
Attempted suicide	KCN	Ingestion	Johnson, Hall, and Rumack
Attempted suicide	KCN	Ingestion	Nakatani et al.
Attempted suicide	KCN	Ingestion	Saincher, Swirsky and Tenenbein
Attempted homicide	“Cyanide”	Ingestion	Chin and Calderon
Attempted suicide	“Cyanide”	Ingestion	Kampe et al.

365 World Health Organization (WHO), *Hydrogen Cyanide and Cyanides: Human Health Aspects*, Concise International Chemical Assessment Document 61 (Geneva: WHO, 2004), 5.

366 The term “lethal dose” is used here, rather than LD_{50}, because the WHO estimate of 1.4 mg/kg is not an LD_{50} but rather is an estimate of the average amount of AC absorbed at death after ingestion of AC.

Exposure Type	Agent	Exposure Route(s)	Source
Accident	AC	Inhalation	Lam and Lau
Accident	KCN	Ingestion	Mannaioni et al.
Attempted suicide	KCN	Ingestion	Weng et al.
Attempted suicide	"Cyanide"	IV	Prieto et al.
Attempted suicide	KCN	Ingestion	Borron et al.
Attempted suicide	KCN	Ingestion	Fortin et al.

Note: See Appendix B for full reference citations.

b. Animal Studies

Human cases qualitatively demonstrate that medical treatment is effective in treating cyanide poisoning, but the data do not support an estimate of PF_{SCAT}. Data from animal studies can be used instead; however, the only data available are far from ideal.

The first problem with the animal data is that the animals were poisoned intravenously with a cyanide salt, instead of by inhalation of AC. Second, in each study, the antidotes were administered either before exposure as a prophylactic or within a minute of the cessation of respiration. The antidote doses were also larger than the modern dose equivalents for a human. Finally, the animals were apparently *not* given supportive care (no mention of such efforts is made in any of the reports). Thus, some consideration is required in the application of the data to humans.

Table 100 summarizes the data as presented by the authors of the journal articles. They tested oxygen, sodium thiosulfate, sodium nitrite, and combinations thereof. Of primary interest for *AMedP-7.5* are the combinations since the combinations would be used in the field. Averaging the results of the best combination of treatments from each report listed in Table 100 yields a PF_{SCAT} of 10, which coincides with *MMCC*'s estimate that the combination of treatments "may save victims exposed to 10 to 20 lethal doses of cyanide."[367] The antidote doses given to the animals were large and given rapidly, indicating that perhaps PF_{SCAT} should be lower than 10. However, the lack of supportive care (which is known to be effective), would indicate that PF_{SCAT} should be higher. Rather than arbitrarily adjusting the number, we suggest using a PF_{SCAT} of 10, which is consistent with *MMCC*.

The effects of the assumptions underlying the proposed PF_{SCAT} are unknown. But since cyanide casualties in the untreated models die within 15 minutes (see Table 98) and the default *AMedP-7.5* value of T_{MTF} is 30 minutes, medical treatment will have no effect for casualties following the Very Severe Injury Profile unless the user elects to change one of the default parameter values.

Table 100. Animal Data Used to Estimate PF_{SCAT} for Humans

367 Hurst et al., *Medical Management of Chemical Casualties*, 58.

Source	Animal	PF_{SCAT} Stated by Authors of Original Reports[a]				
		O_2[b]	$Na_2S_2O_3$[c]	$NaNO_2$[d]	$NaNO_2$[d] & $Na_2S_2O_3$[c]	$NaNO_2$[d] & $Na_2S_2O_3$[c] & O_2[b]
Chen and Rose	Dog	—[e]	3	5	18	—[e]
Way, Gibbon, and Sheehy	Mouse	1.3	4.1	2.5	6.3	8.6
Way et al.	Mouse	1	2.9	1.8	4.4	6.2
Litovitz, Larkin, and Myers	Sheep	2	—[e]	—[e]	5.7	7.3

Note: See Appendix B for full reference citations.

[a] Stated as a ratio of LD_{50}s.

[b] Oxygen treatment.

[c] Sodium thiosulfate treatment.

[d] Sodium nitrite treatment.

[e] No data presented by the authors.

8. MTOR Table

Table 101 is the MTOR table for AC casualties. It is derived from the Injury Profiles and RTD and DOW estimates from clinical case reports.

Medical treatment comprises antidotes and supportive care, but supportive care alone has also been shown to be effective. One effect of medical treatment for the model, as discussed in the paragraphs after Table 101, is that in some cases, patients may be able to RTD faster than if they received no treatment. The primary effect of medical treatment is that if it is provided quickly enough, it can prevent death in casualties who received dosages of up to $10\times LCt_{50}$. Likewise, supportive care alone can prevent death for dosages up to $2\times LCt_{50}$.

As mentioned previously, the default values of $T_{death\text{-}CN\text{-}SL4}$ and T_{MTF} indicate that casualties in the Very Severe cohort will die before medical treatment or supportive care can begin. If the user changes the values, however, the effects of medical treatment or supportive care might become relevant. Thus, Table 101 contains rows related to the Very Severe cohort, with a footnote explaining the caveat related to their use. One row is for casualties whose dosage is dosage greater than or equal to 10 LCt_{50}, and the other is for those whose dosage less than 10 LCt_{50}.

Table 101. AC Medical Treatment Outcome Reporting

Injury Profile	DOW[a]	CONV[a]	RTD[a]
AC Mild	0%	0%	Day 2: 100%
AC Moderate	0%	0%	Day 2: 100%
AC Severe	0%	0%	Day 2: 100%
If casualties receive supportive care without antidote:			

AC Very Severe, $X^{eff}_{AC,ih}$[b] < 5,200[c]	0%	0%	Day 6: 100%
AC Very Severe, $X^{eff}_{AC,ih}$[b] ≥ 5,200[c]	Day 2: 100%	0%	0%
If casualties receive supportive care and antidote:			
AC Very Severe, $X^{eff}_{AC,ih}$[b] < 26,000[c]	0%	0%	Day 4: 100%
AC Very Severe, $X^{eff}_{AC,ih}$[b] ≥ 26,000[c]	Day 2: 100%	0%	0%

[a] Reported values indicate the fraction that changes status on a given day; they are not cumulative.

[b] $X^{eff}_{AC,ih}$ is the Effective CBRN Challenge (dosage) of inhaled AC.

[c] These rows are only used if the user changes the value(s) of $T_{death\text{-}CN\text{-}SL4}$ and/or T_{MTF} such that $T_{MTF} \leq T_{death\text{-}CN\text{-}SL4}$, which will allow casualties in the Very Severe cohort to survive long enough to reach medical treatment. Note that if this change is *not* made, the casualties in the Very Severe cohort will be KIA, so they are not included in the MTOR table.

In the discussions that follow, which explain Table 101, the potential for administrative declaration of asymptomatic "casualties" or delay of RTD for additional monitoring is ignored, consistent with the limitation discussed in Section 0.

Based solely on the Injury Profiles, casualties in the AC Mild and AC Moderate cohorts will recover sufficiently to RTD on Day 1, so they are reported as RTD on Day 2 in the MTOR. Although the AC Severe Injury Profile also indicates RTD on Day 1, we consulted clinical case reports to see if additional information was available.

The analysis on the recovery of the Severe cohort is based on clinical case reports. Since the doses in the reports were unknown and most exposures were not via inhalation, the symptom descriptions were compared to the symptoms in Table 90, and those that matched Severe effects (unconsciousness, breathing irregularities, but without seizures or complete respiratory failure) were considered relevant. We found that case reports varied widely in the degree to which the progression of the patient's symptoms during recovery was reported. In some cases, full recovery was reported within 1 day,[368] consistent with the Injury Profile and its supporting references. In a few other cases that involved intubation of the patient, although extubation was done within 1 day, the patients were not discharged until the second to fifth day. It seems, however, that they were retained for monitoring beyond the point at which all symptoms had vanished (possibly to guard against sequelae related to intubation itself (e.g., secondary infections)).[369] In yet other cases, it is made

368 J. T. B. Bain and E. L. Knowles, "Successful Treatment of Cyanide Poisoning," *British Medical Journal* 2, no. 5554 (1967): 763; Stephen N. Vogel, Thomas R. Sultan, and Raymond P. Ten Eyck, "Cyanide Poisoning," *Clinical Toxicology* 18, no. 3 (1981): 367–383.; Toby L. Litovitz, Robert F. Larkin, and Roy A. M. Myers, "Cyanide Poisoning Treated with Hyperbaric Oxygen," *American Journal of Emergency Medicine* 1, no. 1 (1983): 94–101; Guido Mannaioni et al., "Acute Cyanide Intoxication Treated with a Combination of Hydroxycobalamin, Sodium Nitrite, and Sodium Thiosulfate," *Clinical Toxicology* 40, no. 2 (2002): 181–183.

369 S. Kampe et al., "Survival from a Lethal Blood Concentration of Cyanide with Associated Alcohol Intoxication," *Anaesthesia* 55, no. 12 (2000): 1189–1191; K. K. Lam and F. L. Lau, "An Incident of Hydrogen Cyanide Poisoning," *American Journal of Emergency Medicine* 18, no. 2

clear that consciousness was regained and symptoms were otherwise improving rapidly, but the time until full recovery is not clear.[370]

Although we had expected to find evidence that medical treatment leads to faster recovery than that shown in the Injury Profile, the results in that regard were inconclusive. However, the mixed result from the case reports is consistent with the statements that "most persons arriving for medical care will recover within hours to days"[371] and "those successfully treated after severe effects can return within a day."[372] Although we cannot say with confidence whether there is a clear difference between the results with treatment and the results without treatment, there seems sufficient basis for the model to estimate recovery within 1 day, such that RTD can be reported on Day 2 in the MTOR table.

We used the same general approach to estimate the time to RTD for patients in the Very Severe cohort who receive effective treatment (cases assigned to this cohort had initial symptoms including seizures/convulsions, near or complete lack of breathing, or cardiac arrest), and we encountered the same general problem of case reports providing an inconsistent level of detail regarding the progression of symptoms during recovery. One finding that was different from the case reports assigned to the Severe cohort is that in all but one case assigned to the Very Severe cohort, the patient was intubated (this makes sense, given that one symptom associated with Very Severe in Table 90 is "breathing stops completely").Table 102 summarizes the results from the case reports that actually stated time until discharge. Several other case reports were assigned to the Very Severe cohort, but did not describe the time until discharge.[373] The Table 102 cases are separated based on whether they apply for supportive care only, or full medical treatment.

Given the small number of data points in Table 102, we decided against attempting to assign different time to RTD to different fractions of the Very Severe cohort. For supportive care only, the average time until discharge is 5 days. For full medical treatment, the

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(2000): 172–175; Te-I Weng et al., "Elevated Plasma Cyanide Level after Hydroxocobalamin Infusion for Cyanide Poisoning," *American Journal of Emergency Medicine* 22, no. 6 (2004): 492–493

370 Vogel, Sultan, and Ten Eyck, "Cyanide Poisoning"; Toshio Nakatani et al., "Changes in the Parameters of Oxygen Metabolism in a Clinical Course Recovering from Potassium Cyanide," *American Journal of Emergency Medicine* 11, no. 3 (1993): 213–217; Anurag Saincher, Neil Swirsky, and Milton Tenenbein, "Cyanide Overdose: Survival with Fatal Blood Concentration without Antidotal Therapy," *Journal of Emergency Medicine* 12, no. 4 (1994): 555–557; I. Prieto et al., "Acute Cyanide Poisoning by Subcutaneous Injection," *Emergency Medicine Journal* 22, no. 5 (2005): 389–390.

371 Baskin et al., "Cyanide Poisoning," 386.

372 Hurst et al., *Medical Management of Chemical Casualties*, 61.

373 W. G. Trapp, "Massive Cyanide Poisoning with Recovery: A Boxing-Day Story," *Canadia Medical Association Journal* 102, no. 5 (1970): 517; Robert F. De Busk and Larry G. Seidl, "Attempted Suicide by Cyanide," *California Medicine* 110, no. 5 (1969): 394–396; Johnson, Hall, and Rumack, "Cyanide Poisoning Successfully Treated."

average time is 3.75 days. Although the dataset is small and confidence is therefore low, it does make sense for recovery to be faster with full medical treatment. Both results are consistent with the statement in the *MACW* that "most persons arriving for medical care will recover within hours to days."[374] Consistent with the discharge times mentioned in this paragraph and the rules of *AMedP-7.5* Table 1-4, Table 101 reports RTD on Day 4 for those receiving effective medical treatment and on Day 6 for those receiving effective supportive care.

Table 102. Hospital Discharge Times for Cases Assigned to the Very Severe Cohort

Source	Antidotes Given?	Discharge Time
Graham et al.	No	5 days
Edwards and Thomas	No	7 days
Brivet et al.	No	3 days
Chen and Rose	Yes	6 hours
De Busk and Seidl	Yes	19 hours
Chin and Calderon	Yes	8 days
Fortin et al.	Yes	6 days

Note: See Appendix B for full reference citations.

The final information in the MTOR table is that casualties in the Very Severe cohort with dosage greater than or equal to the threshold for survival (5,400 mg-min/m^3 for supportive care and 27,000 mg-min/m^3 for full medical treatment) are reported as DOW on Day 2. This information is based on the expectation that medical treatment will not be able to save the casualty's life and that they will therefore die on Day 1, which is reported on Day 2, consistent with *AMedP-7.5* Table 1-4.

374 Baskin et al., "Cyanide Poisoning," 386.

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1.12. CK Model
(*AMedP-7.5 Section 4.2.12*)

Introduction

Cyanogen chloride (CK) is a "blood" or systemic chemical agent that was used during WWI[375] and is now often referred to as a TIC because of its use in the chemical industry;[376] however, we refer to it as a chemical agent. CK's primary mechanism of injury is preventing cellular respiration, but it is also an irritant.

The objective of this chapter is to describe the human response model for CK as it has been incorporated into *AMedP-7.5*. The chapter first discusses assumptions for the scope. Then it describes the physiological effects of CK, the toxicity parameters used in *AMedP-7.5*, development of Injury Profiles, and the medical treatment model.

Assumption (*AMedP-7.5 Section 4.2.12.2*)

> **Assumption**: Percutaneous exposure to CK vapour and liquid are negligible.

The percutaneous vapor is assumed negligible because in all the research performed in the development of this model, no sources were found that discussed CK injury resulting from percutaneous vapor exposure (other than ocular effects, which are included in the model). Further, the liquid resulting from a CK attack, and thus the percutaneous liquid contribution to dose, may be neglected due to the agent's high volatility. Finally, FM 3-11.9 lists irritation to the eyes but none to the skin under the heading "skin and eye toxicity" for CK.[377] This assumption may result in an underestimate of the number and severity of casualties.

Physiological Effects (*AMedP-7.5 Tables 4-40 and 4-42*)

The *MACW* states that cyanide poisoning has the same effects no matter the parent compound, but there may be additional effects depending on the parent compound.[378] Few data are available on the effects of CK itself. Typically, they are described in terms of other agents. The *MMCC* states that the "effects of cyanogen chloride include those described for hydrogen cyanide. Cyanogen chloride is also similar to the riot-control agents in causing irritation to the eyes, nose, and airways."[379] Thus, the physiological effects of cyanide poisoning described in the previous chapter apply to CK poisoning. The additional irritant effects of CK are variously described as similar to Cl_2,[380] riot-control agents,[381]

375 Tuorinsky and Sciuto, "Toxic Inhalational Injury," 342 (Table 10-2).
376 Ibid., 343 (Table 10-3).
377 USACMLS, *Chemical/Biological Agents and Compounds*, III-34.
378 Baskin et al., "Cyanide Poisoning," 381.
379 Hurst et al., *Medical Management of Chemical Casualties*, 50.
380 Baskin et al., "Cyanide Poisoning," 381.
381 Hurst et al., *Medical Management of Chemical Casualties*, 50.

lung-damaging agents,[382] or CG specifically.[383] Two military sources[384] indicate that treatment for CK injuries should be a combination of the treatments for AC and CG injuries. The preceding descriptions make sense when one considers the chemical structure of CK (Cl–C≡N): it contains a cyanide moiety (C≡N) and a chlorine moiety (–Cl).

The irritant effects of CK are a function of concentration rather than dosage. At concentrations so low that there is little risk of cyanide toxicity, CK begins causing irritation of the eyes and respiratory system. At higher concentration, the irritation worsens, but the two reports we found that describe controlled human exposure[385] to CK indicate that the irritation never became intolerable, which we interpret as never worse than Injury Severity Level 2. Eventually, as the dosage becomes high enough, the cyanide-related symptoms begin to present, as described in Section 0 for AC, but we found no sources that describe the potency of the irritation at concentrations high enough that the cyanide effects also become relevant. Thus, in Table 104, there are no rows for Severe or Very Severe symptoms.

If the cyanide symptoms are not fatal, CK's irritant nature may produce delayed pulmonary edema, but, at least in animals, "pulmonary injury is difficult or impossible to produce with CK with any degree of regularity."[386] Going further, another source states, "it is evident from the pathological results that the immediate [cyanide-based] paralyzing effect greatly overshadows all others. … all that can be said is that a small extra bonus of casualties and deaths will accrue [from the irritant effects]."[387] It is also worth noting that, as stated in Section 1.B.17, CG's carbonyl group (C=O) causes the acylation reactions that are the primary cause of CG-induced pulmonary edema; however, since CK does not have a carbonyl group, it cannot cause pulmonary edema by the same mechanism (which is reproducible). Based on this information, the CK models do not include pulmonary edema.

Table 103 and Table 104 summarize the preceding qualitative descriptions in a format amenable to use in *AMedP-7.5* and for the analysis presented in this chapter. Consistent with the definition of Injury Profile, the symptom sets are clinically differentiable. Note that Table 103 is a copy of Table 90, since the dosage-based effects of CK are based on its

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382 Ibid., 48.

383 Royal Army, "Cyanogen Agents," 386.

384 Ibid.; U.S. Army Public Health Command (USAPHC), *The Medical CBRN Battlebook*, TG 244 (APG, MD: USAPHC, October 2008), 5-61.

385 R. G. Horton, S. D. Silver, and L. J. Wallen, *Cyanogen Chloride: Eye-Irritant and Lacrimatory Action*, TDMR 603 (Edgewood Arsenal, MD: Chemical Warfare Service, 1943), 3; R. H. D. Short et al., *The Effects of CC on Experimental Animals and on Human Subjects*, PR-2603 (Porton Down, Great Britain: Military Intelligence Division, Chemical Defence Experimental Establishment, 10 March 1944), 6. CBRNIAC-CB-058741.

386 J. M. Coon et al., *Cyanogen Chloride: Special Toxicity Studies*, OSRD 5001 (Washington, DC: Office of Scientific Research and Development, 28 April 1945), 22.

387 Short et al., *The Effects of CC*, 6.

cyanide moiety. It is likely that any CK casualty experiencing cyanide-related symptoms will also experience irritation symptoms. Cyanide and irritation symptoms are listed separately here only to facilitate implementation into the models.

Table 103. Association of CK Injury Severity Levels with Dosage-Dependent CK Symptom Sets

Injury Severity Level	Set of Symptoms
0	No observable injury
1 (mild)	Nausea; fatigue and weakness; transient rapid breathing followed by slower breathing; shortness of breath; excitement; anxiety; dizziness; headache
2 (moderate)	Episodes of vomiting; increased fatigue and weakness; muscle spasms; difficult to breathe; drowsiness
3 (severe)	Severe generalized twitching with or without convulsions; breathing sporadically stops and starts; unconsciousness
4 (very severe)	Convulsions; breathing stops completely; coma

Note: The symptom descriptions in this table are copied from the analogous table for AC (see Table 90).

Table 104. Association of CK Injury Severity Levels with Concentration-Dependent CK Symptom Sets

Injury Severity Level	Set of Symptoms
0	No observable injury
1 (mild)	Ocular and upper respiratory irritation
2 (moderate)	Severe, but not intolerable, ocular and upper respiratory irritation

The next part of the model derivation is to define four sets of toxicity parameters and two concentration thresholds, each associated with a *peak* Injury Severity Level equal to one of the four levels defined in Table 103 or one of the two levels defined in Table 104.

Toxicity Parameters and Concentration Ranges (*AMedP-7.5 Tables 4-40 and 4-42*)

Since CK's effects can be segregated into dosage-based and concentration-based, two subsections are presented. The first addresses dosage-based effects, which are a result of the cyanide moiety of CK, and relate to inhalation only. The second addresses concentration-based effects, which are a result of the chlorine moiety of CK and relate to both inhalation and ocular exposure.

9. Dosage-Based Toxicity Parameters

The CSAC report on CK is FOUO, so it was not used. ECBC-TR-856 reports that for a 2-minute exposure in the healthy population, the LCt_{50} and $ECt_{50\text{-severe}}$ are estimated to be 4700 mg-min/m^3 and 2800 mg-min/m^3, respectively. The probit slope is estimated to be 12.0 probits/log (dose) for both levels of effect,[388] presumably because the same mechanism of toxicity applies at both levels. In terms of dosage-based effects, the same primary mechanism of CK toxicity (cytochrome *c* oxidase inhibition) occurs independently of dosage. The best estimate for the mild and moderate probit slopes for CK is the value of the lethal and severe probit slopes, or 12.0 probits/log (dose).

The only human exposure data identified during our literature review used very low concentrations for testing irritant effects,[389] and no symptoms related to systemic cyanide poisoning were observed; therefore, the data cannot be used to estimate $ECt_{50\text{-mild}}$ or $ECt_{50\text{-moderate}}$. The only animal data we found were used in ECBC-TR-856 to generate toxicity estimates for severe and lethal effects, so they also cannot be used for $ECt_{50\text{-mild}}$ or $ECt_{50\text{-moderate}}$. Consistent with our finding on the lack of human and animal data, the AEGL for CK is "on hold due to insufficient data."[390]

When generating an $ECt_{50\text{-severe}}$ estimate, the authors of ECBC-TR-856 identified a single dataset that provided relevant and usable data. Based on those data, the report gives a calculated ratio of $ECt_{50\text{-severe}}$ to LCt_{50} of 0.60,[391] which is the same ratio reported elsewhere in the report for AC. Since the primary mechanism of toxicity is the same for these agents, it makes sense that the ratios would be equal. Given the lack of other options, we decided to extend the assumption of similar ratios further by using ratios for AC (from Chapter 1.11) to define the $ECt_{50\text{-mild}}$ and $ECt_{50\text{-moderate}}$ for CK. Although we think the this assumption is quite reasonable, one implication is that the assumptions and caveats that apply to the AC $ECt_{50\text{-mild}}$ and $ECt_{50\text{-moderate}}$ also apply to the analogous CK values reported in Table 105. Specifically, the ratio of $ECt_{50\text{-moderate}}$ for AC was estimated to be 0.75 (see Table 96), so the estimated $ECt_{50\text{-moderate}}$ for CK is $2800 \times 0.75 = 2100$ mg-min/m^3. Similarly, the ratio of the AC $ECt_{50\text{-mild}}$ to $ECt_{50\text{-severe}}$ is 700/1600 = 0.4375 (Table 97), so the estimated $ECt_{50\text{-mild}}$ for CK is $2800 \times 0.4375 = 1225 \approx 1200$ mg-min/m^3. The values are rounded to two significant digits because of the high uncertainty. The final set of median toxicities and probit slopes for inhaled CK is summarized in Table 105.

Table 105. Median Toxicities and Probit Slopes for Inhaled CK

388 Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*, C-1 and C-7.

389 Horton, Silver, and Wallen, *Cyanogen Chloride*; Short et al., *The Effects of CC*.

390 EPA Website, "Acute Exposure Guideline Levels (AEGLs) Values," updated on October 1, 2015, http://www.epa.gov/aegl/access-acute-exposure-guideline-levels-aegls-values#tab-4.

391 Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*, C-9.

Injury Profile	Effect	Median Toxicity[a] (mg-min/m^3)	Probit Slope (Probits/Log (dose))
CK Very Severe	Lethal	4700	12.0
CK Severe	Severe	2800	12.0
CK Moderate	Moderate	2100	12.0
CK Mild	Mild	1200	12.0

[a] The median toxicity is an estimate for a 2-minute exposure.

10. Concentration Thresholds

Two reports provide information on CK's irritant effects as a function of concentration. In the first report,[392] two of six soldiers experienced "slight irritation" of the eyes beginning at concentrations around 1 mg/m^3. Severe lacrimation and slight irritation of the upper respiratory system occurred immediately at 17 mg/m^3. The subjects donned goggles and were exposed to concentrations of 45 mg/m^3, 95 mg/m^3, 175 mg/m^3, and 384 mg/m^3 for up to 1 minute. They experienced progressively worse upper respiratory irritation, but it never became "intolerable," which we interpret as never worse than Injury Severity Level 2. The second report[393] provides similar information based on tests using concentrations of 6 mg/m^3 to about 100 mg/m^3.

Based on this information, the model will use a lower concentration boundary of 1 mg/m^3 for "mild" effects. The lower boundary for "moderate" effects is 20 mg/m^3, rounded up from 17 mg/m^3, the concentration at which the eye irritation was so severe that the soldiers donned eye protection for the remaining tests. Table 106 summarizes the CK concentration ranges.

Table 106. CK Concentration Ranges

Injury Profile[a]	Concentration Range (mg/m^3)
(none)	< 1
[CK] Mild	1 – < 20
[CK] Moderate	≥ 20

[a] The symbol [CK] is used to refer to CK concentration-based effects, to distinguish these Injury Profiles from those in Table 105. These effects are from both inhalation and ocular exposure.

Injury Profiles (*AMedP-7.5 Tables 4-41 and 4-43*)

The framework of the *AMedP-7.5* methodology is such that there must be separate Injury Profiles for dosage-based and concentration-based effects. No available case reports or military studies describe symptoms of, or recovery from, the cyanide effects of CK poisoning. Consistent with earlier discussion in this chapter on the similarities between AC and CK, we assumed that the progression of symptoms over time would also be the same,

392 Short et al., *The Effects of CC*, 6.

393 Horton, Silver, and Wallen, *Cyanogen Chloride*, 3.

and on that basis, the dosage-based Injury Profiles for CK (see Table 107) are the same as the AC Injury Profiles (see Table 98).

The Injury Profiles for concentration-based effects are based on the same two sources used to determine the concentration ranges. Both sources indicate that the onset of symptoms is nearly immediate.[394] Only one source describes recovery. In an experiment that exposed 27 soldiers to 100 mg/m^3, "subjects experienced almost complete relief within 2 minutes of the end of exposure, and showed slight congestion of the bulbar conjunctiva for about 10 minutes."[395] On this basis, the [CK] Mild Injury Profile decreases from Injury Severity Level 1 to 0 at 2 minutes, and the Moderate Injury Profile decreases from Injury Severity Level 2 to 1 at 2 minutes and Injury Severity Level 1 to Injury Severity Level 0 at 10 minutes.

Table 107 and Table 108 summarize the CK Injury Profiles.

394 Short et al., *The Effects of CC*, 4; Horton, Silver, and Wallen, *Cyanogen Chloride*, 3.

395 Horton, Silver, and Wallen, *Cyanogen Chloride*, 4.

Table 107. Inhaled CK Injury Profiles

Time Point (min)	CK Mild	CK Moderate	CK Severe	CK Very Severe
1	1	2	3	4
10	1	1	2	4
15	1	1	2	4[a]
120	0	1	1	
180	0	0	1	
480	0	0	0	

[a] Death is modeled to occur at this point, based on the default value of the parameter $T_{death\text{-}CN\text{-}SL4}$ in *AMedP-7.5*.

Table 108. Peak CK Concentration Injury Profiles

Time Point (min)	[CK] Mild	[CK] Moderate
1	1	2
2	0	1
10	0	0

Medical Treatment (*AMedP-7.5 Table 4-44*)

11. Efficacy of Medical Treatment

For the cyanide effects, medical treatment is the same as for AC, so the PF_{SC} and PF_{SCAT} values (2 and 10, respectively) derived in Subsection 1.B.7 are also applied to CK. The caveats related to T_{MTF} and $T_{death\text{-}CN\text{-}SL4}$ also apply.

The initial irritant (concentration-based) effects recede quickly and spontaneously, as indicated by the Injury Profiles in Table 108. Given the rapid recovery, medical treatment for these effects will likely not be needed, and, if it is, it will comprise only nonspecific palliative care and is unlikely to significantly alter the course of recovery.

12. MTOR Table

Table 109 is the MTOR table for CK casualties. Since both [CK] Injury Profiles (Table 108) show faster recovery to Injury Severity Level 0 than every CK Injury Profile, the dosage-based effects of CK are dominant in terms of estimating medical treatment outcomes. Therefore, Table 109 does not mention [CK] Injury Profiles. Since only the dosage-based effects determine outcomes, Table 109 is modeled after the AC MTOR table (see Table 101), the supporting discussion for which is not repeated here (see Subsection 1.B.8). The only differences between the two tables are the dosage thresholds related to the Very Severe cohorts. The values are different because the LCt_{50}s are different.

Table 109. CK Medical Treatment Outcome Reporting

Injury Profile	DOW	CONV	RTD
CK Mild	0%	0%	Day 2: 100%
CK Moderate	0%	0%	Day 2: 100%
CK Severe	0%	0%	Day 2: 100%
If casualties receive supportive care without antidote:			
CK Very Severe, $X^{eff}_{CK,ih}$[b] < 9,400[c]	0%	0%	Day 6: 100%
CK Very Severe, $X^{eff}_{CK,ih}$[b] ≥ 9,400[c]	Day 2: 100%	0%	0%
If casualties receive supportive care and antidote:			
CK Very Severe, $X^{eff}_{CK,ih}$[b] < 47,000[c]	0%	0%	Day 4: 100%
CK Very Severe, $X^{eff}_{CK,ih}$[b] ≥ 47,000[c]	Day 2: 100%	0%	0%

[a] Reported values indicate the fraction that changes status on a given day; they are not cumulative.

[b] $X^{eff}_{CK,ih}$ is the Effective CBRN Challenge (dosage) of inhaled CK.

[c] These rows are only used if the user changes the value(s) of $T_{death\text{-}CN\text{-}SL4}$ and/or T_{MTF} such that $T_{MTF} \leq T_{death\text{-}CN\text{-}SL4}$, which will allow casualties in the Very Severe cohort to survive long enough to reach medical treatment. Note that if this change is *not* made, the casualties in the Very Severe cohort will be KIA, so they are not included in the MTOR table.

1.13. H_2S Model

(*AMedP-7.5 Section 4.2.13*)

Introduction

Hydrogen sulfide (H_2S) acts on humans by the same mechanism as AC and other cyanides. In that sense, it can also be called a "blood" or systemic chemical agent. Although it is more often thought of as a TIC because of its use in the chemical industry,[396] it was used during WWI, so we refer to it as a chemical agent. Like AC, H_2S's primary mechanism of injury is preventing cellular respiration. Like CK, it is also a respiratory and ocular irritant.

The objective of this chapter is to describe the human response model for H_2S as it has been incorporated into *AMedP-7.5*. The chapter first discusses assumptions for the scope. Then it describes the physiological effects of H_2S, the toxicity parameters used in *AMedP-7.5*, development of Injury Profiles, and the medical treatment model.

Assumption (*AMedP-7.5 Section 4.2.13.2*)

> **Assumption**: Percutaneous exposure to H_2S vapour and liquid are negligible.

The percutaneous vapor dosage required to produce symptoms is several orders of magnitude higher than the inhalation dosage required to produce symptoms,[397] and the boiling point is so low (–60 °C) that liquid H_2S is not operationally relevant. FM 3-11.9 does not contain information on H_2S.

Physiological Effects[398] (*AMedP-7.5 Table 4-45*)

> **Note**: Although it is recognized that endogenously produced H_2S has several beneficial physiological functions,[399] the focus of this chapter is on intoxication by exogenously produced H_2S.

The most well-understood effect of H_2S is its inhibition of cytochrome *c* oxidase, similar to the dominant effect of cyanide (see Section 0). For this reason, most of the

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396 Tuorinsky and Sciuto, "Toxic Inhalational Injury," 342 (Table 10-3).

397 Walter Schütze, "Über die Gefährdung von Mensch und Tier durch Große Konzentrationen einiger giftiger Gase von der Haut aus [On the Risks to Humans and Animals by Dermal Exposures to High Concentrations of Some Toxic Gases]," *Archiv für Hygiene und Bakteriologie* 98 (1927): 78.

398 This section is mostly paraphrased from the following three sources: Agency for Toxic Substances and Disease Registry, *Draft Toxicological Profile for Hydrogen Sulfide and Carbonyl Sulfide* (Atlanta, GA: ATSDR, October 2014), 15–19 and 111–113; National Research Council, "Hydrogen Sulfide: Acute Exposure Guideline Levels," vol. 9 of *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (Washington, DC: The National Academies Press, 2010), 177–179 and 195–197; R. O. Beauchamp et al., "A Critical Review of the Literature on Hydrogen Sulfide Toxicity," *CRC Critical Reviews in Toxicology* 13, no. 1 (1984): 25–97.

399 Agency for Toxic Substances and Disease Registry, *Draft Toxicological Profile*, 16.

symptoms of H_2S poisoning are the same as those of cyanide poisoning, as is the general trend in symptoms with increasing dosage: as total dosage increases the victim may experience fatigue, dizziness, dyspnea, anxiety, nausea and vomiting, muscle spasms, unconsciousness, apnea, convulsions, and coma. Like cyanide, H_2S also likely has lesser effects related to its inhibition of other enzymes, but this chapter (and most of the literature) focuses on effects related to cytochrome *c* oxidase inhibition. Different from cyanide, H_2S also has what is colloquially referred to as its "slaughterhouse sledgehammer" or "knockdown" effect, whereby individuals are rendered unconscious upon taking one or two breaths of gas that has high H_2S concentration (faster than that which occurs with cyanides). Most sources either imply or directly state that knockdown is a result of cytochrome *c* oxidase inhibition, which seems somewhat odd given the relative rapidity of the effect; however, for this chapter, the exact mechanism of knockdown is not important, so we will not attempt to describe it further. Some H_2S reports state that the systemic effects of H_2S are concentration dependent, citing the rapid destruction of H_2S in the human body as evidence, but such self-detoxification only indicates that H_2S does not follow Haber's law, not that its effects are concentration-dependent. This paper treats all systemic effects of H_2S as dosage dependent, consistent with the cyanide-based models for AC and CK.

The second major effect of H_2S is irritation and inflammation of the mucous membranes of the eyes and respiratory tract. Although one might expect that the irritation symptoms are a function of concentration rather than dosage, the best source of original data that we found[400] indicates that the symptoms do not appear instantly upon exposure, so the model does not include a concentration-based component. Irritation symptoms are grouped with the systemic symptoms as part of the dosage-dependent model.

At low concentrations, H_2S is primarily observable by the characteristic odor of rotten eggs. As the concentration and exposure time increase, the eyes and respiratory tract become irritated. For the eyes, this irritation can lead to keratoconjuncitivitis (sometimes referred to as "gas-eye"). Symptoms include lacrimation with a "gritty" feeling, photophobia, and burning eyes. In severe cases, erosion and/or ulceration of the cornea may occur. Respiratory irritation begins with pain, difficulty breathing, and coughing. In more severe cases involving high concentrations or long exposure times, delayed (non-cardiogenic) pulmonary edema can occur, but there is argument in the literature about whether this is a typical effect.[401] Most of that argument is qualitative or based on a small

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400 R. R. Sayers et al., *Investigation of Toxic Gases from Mexican and Other High-Sulphur Petroleums and Products*, Bulletin 231 (Washington, DC: Bureau of Mines, Department of the Interior, 1925), 60–63.

401 Thomas H. Milby and Randall C. Baselt, "Hydrogen Sulfide Poisoning: Clarification of Some Controversial Issues," *American Journal of Industrial Medicine* 35, no. 2 (1999): 192–195; T. L. Guidotti, "Hydrogen Sulphide," *Occupational Medicine* 46, no. 5 (1996): 367–371; Bassam Doujaiji and Jaffar A. Al-Tawfiq, "Hydrogen Sulfide Exposure in an Adult Male," *Annals of Saudi Medicine* 30, no. 1 (2010): 76–80; Howard W. Haggard, "The Toxicology of Hydrogen Sulphide,"

dataset; however, Burnett et al. summarized 221 cases of H_2S poisoning that occurred in Canadian gas and oil fields between 1969 and 1973. Of these cases, 173 victims were brought to a hospital, and only 20% of them were found to have pulmonary edema.[402] On this basis, we concluded that pulmonary edema is not a typical effect, and it should therefore not be included in the model.

Some sources also indicate that pneumonia can be a delayed effect, but since this effect is thought to be a secondary consequence related to "the inhibitory effect of H_2S on the alveolar macrophages and their subsequent inability to inactivate bacteria,"[403] pneumonia is not included in the model.

One important topic not addressed in most of the literature is how severe the irritation symptoms become at dosages that also cause systemic effects, particularly in reference to whether these symptoms could prevent a soldier from carrying out the mission at dosages at which the systemic symptoms would not. One source indicates, that at lower concentrations for an unspecified exposure duration, the irritation symptoms primarily revolve around keratoconjuncitivitis and at higher concentrations, the primary effect is delayed pulmonary edema (if it occurs).[404] The ocular irritation presumably does not worsen to the point of functional blindness, for example.

Finally, H_2S poisoning sometimes results in neurological sequelae,[405] but the literature does not provide sufficient data to determine the dosage dependence or frequency. The NRC notes, "[n]umerous other reports of permanent or persistent neurologic effects after exposure to H_2S have been published …. As with the other case studies, these reports lack definitive exposure measurements."[406] Another expert reviewer states, "In a small percentage of victims, primarily those who are very severely poisoned or who are not promptly rescued, prolonged apnea can lead to hypoxic encephalopathy with sequelae ranging from mild neurological deficit to hypoxia-related dementias or death."[407] The models presented in this chapter do not include sequelae.

Journal of Industrial Hygiene 7, no. 3 (1925): 113–121; Beauchamp et al., "A Critical Review of the Literature on Hydrogen Sulfide Toxicity."

402 W. W. Burnett et al., "Hydrogen Sulfide Poisoning: Review of 5 Years' Experience," *Canadian Medical Association Journal* 117, no. 11 (1977): 1278.

403 R. J. Reiffenstein, William C. Hulbert, and Sheldon H. Roth, "Toxicology of Hydrogen Sulfide," *Annual Review of Pharmacology and Toxicology* 32 (1992): 109–134, 119.

404 Guidotti, "Hydrogen Sulphide," 368.

405 Beauchamp et al., "A Critical Review of the Literature on Hydrogen Sulfide Toxicity," 38.

406 National Research Council, "Hydrogen Sulfide," 180.

407 Thomas H. Milby, "Hydrogen Sulfide and Sulfur Dioxide: Basic Toxicology and Primary Litigation Issues," last modified May 2005, http://www.experts.com/Articles/Hydrogen-Sulfide-and-Sulfur-Dioxide-Basic-Toxicology-and-Primary-Litigation-Issues-By-Thomas-H-Milby-MD.

Table 110 summarizes the previous qualitative descriptions in a format amenable to use in *AMedP-7.5* and for the analysis presented in this chapter.

Table 110. Association of H_2S Injury Severity Levels with H_2S Symptom Sets

Injury Severity Level	Set of Symptoms
0	No observable injury
1 (mild)	Nausea; fatigue and weakness; transient rapid breathing followed by slower breathing; shortness of breath; excitement; anxiety; dizziness; headache; gritty feeling in eyes; lacrimation; respiratory irritation; olfactory paralysis; cough
2 (moderate)	Episodes of vomiting; increased fatigue and weakness; muscle spasms; difficult to breathe; drowsiness; severe eye irritation; blurry vision; sensitivity to light; stronger respiratory irritation
3 (severe)	Severe generalized twitching with or without convulsions; breathing sporadically stops and starts; unconsciousness
4 (very severe)	Convulsions; breathing stops completely; coma

Note: The systemic effect-related symptom descriptions in this table are copied from the analogous table for AC (Table 90).

Toxicity Parameters (*AMedP-7.5 Table 4-45*)

No CSAC report has been published for H_2S. ECBC-TR-856 reports an LCt_{50} of 3200 mg-min/m^3 with a probit slope of 18.0 probits/log (dose). It also reports an $ECt_{50\text{-severe}}$ of 2200 mg-min/m^3 with a probit slope of 18.0 probits/log (dose).

The remaining question is what values should be used for the moderate and mild effect levels. To estimate the parameters, we first conducted a literature search, beginning with ECBC-TR-856, the AEGL document for H_2S,[408] and two other summary or review reports,[409] and the sources each report cited. This search showed that although there are many case reports of human exposures, there is rarely any quantifiable dose or dosage estimate because the exposure concentration or time are unknown. Further, most information from animal experiments relates to lethal or severe effects. However, a few reports include dosage estimates for human exposures for mild and moderate effects: a series of controlled experimental studies by Bhambhani et al. conducted during the

408 National Research Council, “Hydrogen Sulfide.”

409 Agency for Toxic Substances and Disease Registry, *Draft Toxicological Profile*; Beauchamp et al., “A Critical Review of the Literature on Hydrogen Sulfide Toxicity.”

1990s[410] and a 1925 report on the investigation of toxic gases related to petroleum products (including H_2S) by the Bureau of Mines.[411]

None of the data identified in the literature search were usable for estimating probit slopes. ECBC-TR-856 states that the probit slope derived from lethality data (18.0 probits/log (dose)) was applied for severe effects. Applying the same slope for lower symptom severity may be questionable for H_2S, depending on whether irritation or systemic symptoms are dominant; however, given the lack of data, there appears to be no other option, so a slope of 18.0 probits/log (dose) is used for the mild and moderate toxicity curves. We now turn to the estimation of median toxicities.

All the Bhambhani experiments involved healthy, young (approximately 20 to 30 years old) subjects riding a graded exercise bicycle while breathing air mixed with a known concentration of H_2S for a pre-determined time. In all cases, none of the subjects reported adverse health effects after their exposure, so these data are useful for setting a lower limit for $ECt_{50\text{-mild}}$, as explained below. Table 111 summarizes the Bhambhani et al. data and provides a calculated EPD for each dataset. Because the subjects were exercising, the minute volume must be considered in calculations, which was done by multiplying the EPD calculated via Eq. 4 by the ratio of the maximum reported minute volume divided by 15 L/min.[412] The TLE used in the calculations is 5.7.[413]

The value from Table 111 that is most useful for this TRM is the calculated EPD for the men in the 1997 study, who had the highest EPD at 169 mg-min/m^3. For estimating a minimum $ECt_{50\text{-mild}}$, we can set 169 mg-min/m^3 equal to the $ECt_{01\text{-mild-min}}$ and use the previously assumed probit slope of 18.0 probits/log (dose) to estimate that $ECt_{50\text{-mild-min}}$ is ~230 mg-min/m^3. The true $ECt_{50\text{-mild}}$ is likely to be higher. Although this estimation

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410 Yagesh Bhambhani et al., "Comparative Physiological Responses of Exercising Men and Women to 5 ppm Hydrogen Sulfide Exposure," *American Industrial Hygiene Association Journal* 55, no. 11 (1994): 1030–1035; Yagesh Bhambhani et al., "Effects of 5 ppm Hydrogen Sulfide Inhalation on Biochemical Properties of Skeletal Muscle in Exercising Men and Women," *American Industrial Hygiene Association Journal* 57, no. 5 (1996): 464–468; Yagesh Bhambhani and Mohan Singh, "Physiological Effects of Hydrogen Sulfide Inhalation during Exercise in Healthy Men," *Journal of Applied Physiology* 71, no. 5 (1991): 1872–1877; Yagesh Bhambhani et al., "Effects of 10-ppm Hydrogen Sulfide Inhalation on Pulmonary Function in Healthy Men and Women," *Journal of Occupational and Environmental Medicine* 38, no. 10 (1996): 1012–1017; Yagesh Bhambhani et al., "Effects of 10-ppm Hydrogen Sulfide Inhalation in Exercising Men and Women: Cardiovascular, Metabolic, and Biochemical Responses," *Journal of Occupational and Environmental Medicine* 39, no. 2 (1997): 122–129.

411 Sayers et al., *Investigation of Toxic Gases*.

412 The maximum breathing was used instead of the average because the purpose of using the Bhambhani data in this analysis is to set a minimum value for toxicity parameters and we want the highest EPD that can be calculated from the data. 15 L/min was used as the denominator for the ratio because it is the typically assumed minute volume for inhalation toxicity parameters.

413 Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*, I-12.

provides a potentially useful lower bound, the Bhambhani et al. data cannot help any further in defining the needed toxicity parameters.

Table 111. Summary of Bhambhani Data and Associated Calculated EPDs

Publication Year[414]	Subjects	Concentration (mg/m^3)[a,b]	Duration (min)[a]	Reported Max Minute Volume (L/min)	Calculated EPD ($mg\text{-}min/m^3$)
1991	16 men	7	16	(none)	–
1994 1996a	13 men 12 women	7	30	54.0 (men) 48.9 (women)	81 (men) 73 (women)
1996b	9 men 10 women	14	15	45 (men) 32 (women)	120 (men) 85 (women)
1997	15 men 13 women	14	30	56.4 (men) 41.4 (women)	169 (men) 124 (women)

[a] The maximum values tested are listed here since the purpose is to determine the highest challenge that resulted in no symptoms.

[b] Concentrations were converted from parts per minute to milligrams per cubic meter using the following: 1 ppm = 1.4 mg/m^3.

The Bureau of Mines report includes a table[415] describing symptoms in humans after exposure to concentrations of 140 to 630 mg/m^3 for 2 minutes to 1 hour. The authors did not publish the record of individual experiments or accidents that enabled them to create the table, but it is clear that actual human exposures, not animal testing, were their data source.[416] Table 112 reproduces the relevant observations recorded in the Bureau of Mines report's table, with the H_2S concentration converted to milligrams per cubic meter. To calculate standard dosage (assuming Haber's rule), simply multiply a concentration (leftmost column) with a time (top row). Approximate EPD ranges, as calculated by Eq. 4,[417] are listed in italics in each box, along with the associated symptom descriptions from the Bureau of Mines report. Note how different the standard dosages are from the EPD estimates. This difference points to the necessity of not assuming Haber's rule.

414 1991: Bhambhani and Singh, "Physiological Effects of Hydrogen Sulfide Inhalation"; 1994: Bhambhani et al., "Comparative Physiological Responses of Exercising Men and Women to 5 ppm Hydrogen Sulfide Exposure"; 1996a: Bhambhani et al., "Effects of 5 ppm Hydrogen Sulfide Inhalation on Biochemical Properties"; 1996b: Bhambhani et al., "Effects of 10-ppm Hydrogen Sulfide Inhalation on Pulmonary Function"; 1997: Bhambhani et al., "Effects of 10-ppm Hydrogen Sulfide Inhalation in Exercising Men and Women."

415 Sayers et al., *Investigation of Toxic Gases*, 70.

416 The dog data also presented in the source were not used to derive the model documented in this TRM.

417 In Table 112, C_1 is the concentration in the leftmost column; t_1 is the exposure duration listed in the top row; and n is the TLE, which is 5.7 for H_2S according to Sommerville, Channel, and Bray, *Proposed Provisional Human Toxicity Estimates*, I-12.

EPD estimates in Table 112 are given to four significant digits because, as described below, the values are used for further calculations, and we prefer to round only at the end (to avoid rounding errors). Cells with a blue background describe symptoms that correlate well with Injury Severity Level 1, and cells with a green background describe symptoms correlate well with Injury Severity Level 2. Note that despite the categorization based on symptoms, the EPD estimates for some of the blue and green cells overlap. The overlap indicates that we should have low confidence in these data. Since these data are the only data available, however, we have to use them if we are to estimate toxicity parameters.

Table 112. Effect of Exposures as Described by Sayers et al.

H_2S Concentration (mg/m^3)	Column A 2 to 15 minutes	Column B 15 to 30 minutes	Column C 30 minutes to 1 hour
Row 1 140 to 210	*280.0–598.1 mg-min/m³* Coughing; irritation to eyes, loss of sense of smell	*398.7–675.4 mg-min/m³* Disturbed respiration; pain in eyes; sleepiness	*450.3–762.8 mg-min/m³* Throat irritations
Row 2 210 to 280	*420.0–797.5 mg-min/m³* Loss of sense of smell	*598.1–900.6 mg-min/m³* Trachea and eye irritation	*675.4–1017 mg-min/m³* Eye and trachea irritation
Row 3 350 to 490	*700.0–1396 mg-min/m³* Irritation of eyes; loss of sense of smell	*996.8–1576 mg-min/m³* Irritation of eyes	*1126–1780 mg-min/m³* Painful secretion of tears; weariness
Row 4 490 to 630	*980.0–1794 mg-min/m³* Irritation of eyes; loss of sense of smell	*1396–2026 mg-min/m³* Difficult respiration; coughing; irritation of eyes	*1576–2288 mg-min/m³* Increased irritation to eyes and nasal tract; dull pain in head; weariness; light shy

Note: The italics in each cell give the approximate EPD range as calculated by Eq. 4. These ranges do not equate to standard dosage calculations.

The only somewhat reasonable approach that we could imagine for estimating median toxicities was to determine a value that corresponds to the bottom end of each toxicity curve and then estimate the median toxicity based on that value and the previously assumed probit slope of 18.0 probits/log (dose). For example, 280.0 mg-min/m^3 is the lowest estimated EPD that led to Mild symptoms, and if $ECt_{01\text{-mild}}$ = 280 mg-min/m^3, then based on the probit slope stated above, $ECt_{50\text{-mild}}$ = 376 mg-min/m^3. Since the method by which this estimate was generated engenders so little confidence, the final recommendation is rounded to one significant digit (400 mg-min/m^3). Following the same process, but based on 1126 mg-min/m^3 being the lowest estimated EPD that led to Moderate symptoms, the $ECt_{50\text{-moderate}}$ estimate is 1515 mg-min/m^3, rounded to 1500 mg-min/m^3 for the model (see Table 113).

An $ECt_{50\text{-mild}}$ estimate of 400 mg-min/m^3 is consistent with the findings from the Bhambhani experiments. $ECt_{01\text{-mild}}$ is then ~300 mg-min/m^3, which would lead one to expect that none of Bhambhani's subjects should experience symptoms, which is consistent with the experimental results. On the other hand, note that most of the symptoms listed in Table 112 are irritation related, which raises the question of whether it is acceptable to use the probit slope of 18 probits/log (dose) for estimates based on the Table 112 data. There is no obvious solution, so we can only repeat the reasoning given previously: with the data that are available, there is no alternative probit slope estimate. Also, if a lower probit slope were used, the $ECt_{01\text{-mild}}$ estimate would be lower, and the mild toxicity model proposed here would then be *less* consistent or possibly inconsistent with the Bhambhani results.

The final set of median toxicities and probit slopes for inhaled H_2S is summarized in Table 113. To emphasize, high uncertainty surrounds the mild and moderate ECt_{50}s and probit slopes, but, given the poor quality of the data, these are the best estimates available. However, when possible, new values based on better supporting data should be derived and used in *AMedP-7.5* (or perhaps its successor).

Table 113. Median Toxicities and Probit Slopes for Inhaled H_2S

Injury Profile	Effect	Median Toxicity[a] (mg-min/m^3)	Probit Slope (Probits/Log (dose))
H_2S Very Severe	Lethal	3200	18.0
H_2S Severe	Severe	2200	18.0
H_2S Moderate	Moderate	1500	18.0
H_2S Mild	Mild	400	18.0

[a] The median toxicity is an estimate for a 2-minute exposure.

Injury Profiles (*AMedP-7.5 Table 4-46*)

The general reputation of H_2S for acute exposures is that the effects appear quickly, similar to cyanide. One study has shown that the affinities of cyanide and hydrosulfide for cytochrome *c* oxidase binding sites are of the same order of magnitude.[418] Thus, because the definition of time zero in *AMedP-7.5* is at the cessation of exposure, each Injury Profile begins at its highest severity. The problem then becomes determining the progression of the Injury Profile over time as survivors recover.

Few quantitative data are available to inform models of recovery time for H_2S symptoms. The most prevalent data are generic and qualitative claims: two widely cited and otherwise thorough reviews say very little on the issue of human recovery after

418 R. Wever, B. F. van Gelder, and D. V. Dervartanian, "Biochemical and Biophysical Studies on Cytochrome C Oxidase. XX. Reaction with Sulphide," *Biochimica et Biophysica Acta* (*BBA*) - *Bioenergetics* 387, no. 2 (1975): 189–193, 192.

exposure.[419] The Bureau of Mines report cited previously also does not give any quantifiable recovery information. However, we did find a few case reports of recovery after human exposure that were useful. These reports are cited in the discussion that follows.

As for animal data, we identified many sublethal toxicity studies on rats, mice, rabbits, and monkeys.[420] Unfortunately, the original report on the monkey experiments does not include data usable for this purpose. The experiments focused on lethality, and relatively little information was presented. Most of the other animal data relate to exposures of 4 hours or longer (the more "acute" studies tend to relate to lethality testing). Further, it is not clear that rats, mice, or rabbits are good models of human recovery from H_2S poisoning. We deemed none of the animal data we found to be relevant for developing Injury Profiles.

Although the generic and qualitative statements regarding human recovery are not sufficient, they are a useful starting point. The following statements are a selection to give the reader a general sense of the recovery process and of the lack of specificity in the literature.

> Following acute exposure to high concentrations of H_2S, an affected person may have a rapid and complete recovery if promptly removed from the hazardous area and artificial respiration applied.[421]
>
> Most victims, even though they may be unconscious, appear to recover spontaneously if they are breathing.[422]
>
> Lacrimation, photophobia, corneal opacity, tachypnea, dyspnea, tracheo-bronchitis, nausea, vomiting, diarrhea, and cardiac arrhythmias … generally resolve on evacuation to fresh air.[423]
>
> In acute cases, if there was recovery, it was rapid, and only rarely were any after effects apparent for more than a few hours.[424]

Because both H_2S and cyanide exert injury by action on cytochrome *c* oxidase, we used the progressions from AC Injury Profiles to fill in certain gaps and as a check on the proposed parameters for H_2S. One known difference between the two agents is that the dissociation constant of sulfmethemoglobin is two orders of magnitude higher than that for

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419 Beauchamp et al., "A Critical Review of the Literature on Hydrogen Sulfide Toxicity"; Reiffenstein, Hulbert, and Roth, "Toxicology of Hydrogen Sulfide."

420 Most of which are summarized in Section 3.2.1 of the H_2S AEGL report: National Research Council, "Hydrogen Sulfide," 189–193.

421 Beauchamp et al., "A Critical Review of the Literature on Hydrogen Sulfide Toxicity," 38.

422 Reiffenstein, Hulbert, and Roth, "Toxicology of Hydrogen Sulfide," 128.

423 National Research Council (NRC), *Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants*, vol. 3 (Washington, DC: The National Academies Press, 2009), 112.

424 Sayers et al., *Investigation of Toxic Gases*, 74.

cyanmethemoglobin,[425] which indicates that recovery from the systemic effects of H_2S poisoning may be faster than recovery from AC poisoning.

Only one data point is available for estimating the progression of Mild injury. One case report states that the symptoms of a man who had "eye, nose, and throat irritation … disappeared after an hour."[426] This recovery is faster than the AC Mild Injury Profile (recovery at 2 hours) and consistent with the last sentence of the previous paragraph. Thus, it seems reasonable to model recovery from Injury Severity Level 1 to Injury Severity Level 0 at 1 hour for the Mild Injury Profile. Since the reporting resolution of *AMedP-7.5* is 1 day, the exact number of hours is not very important, so long as it is less than 1 day.

For the Moderate Injury Profile, we again found only one source that provides usable information. The same case report as cited previously also states that 10 men had nausea, vomiting, itchy eyes, and nose irritation. Because of the vomiting, their symptoms align better with the Moderate Injury Profile (see Table 110). They "recovered without complications after a few hours,"[427] which we interpret as Injury Severity Level 0 at either 2 or 3 hours. Since recovery from Mild symptoms was faster than that for AC, we assumed recovery from Moderate symptoms would also be faster and chose 2 hours for the total recovery time. As for when the Injury Severity Level decreases from 2 to 1, we found no relevant data, so the value from the AC Moderate Injury Profile (10 minutes) is applied to H_2S. Again, the exact values are not of critical importance because of the 1-day reporting resolution of *AMedP-7.5*.

For the Severe Injury Profile, we found many reports that describe exposure leading to unconsciousness followed by prompt regaining of consciousness once rescuers moved the victim to fresh air.[428] However, almost all such reports did not provide specific times until the victims recovered. With regard to the duration of unconsciousness, two reports provided details: one stated the duration for nine patients to be between 5 seconds and 3

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425 Roger P. Smith, "Toxic Responses of the Blood," in *Cassarett and Doull's Toxicology: The Basic Science of Poisons*, 5th ed, ed. Curtis D. Klaassen (New York: MacMillan, 1996), 352.

426 Olga Parra et al., "Inhalation of Hydrogen Sulphide: A Case of Subacute Manifestations and Long Term Sequelae," *British Journal of Industrial Medicine* 48, no. 4 (1991): 286.

427 Ibid.

428 For example: L. J. Hurwitz and Gweneth I. Taylor, "Poisoning by Sewer Gas with Unusual Sequelae," *The Lancet* 253, no. 6822 (1954): 1110–1112; 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; Burnett et al., "Hydrogen Sulfide Poisoning: Review"; 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; Beauchamp et al., "A Critical Review of the Literature on Hydrogen Sulfide Toxicity"; Milby, "Hydrogen Sulfide and Sulfur Dioxide"; Sayers et al., *Investigation of Toxic Gases*; Reiffenstein, Hulbert, and Roth, "Toxicology of Hydrogen Sulfide."

minutes,[429] and another stated that four patients were unconscious for between 2 and 20 minutes.[430] Based on these reports, the Severe Injury Profile includes recovery from Injury Severity Level 3 to Injury Severity Level 2 at 10 minutes (approximately the mid-range value). Neither report gave any other quantitative information on the victims' recovery.

Another source gave information on an individual's recovery after regaining consciousness. A single victim became unconscious at a work site and arrived at the hospital 30 minutes later. Although he was treated with several supposed antidotes, they were administered so late that there is no reason to expect they had any effect on the patient's outcome (see Section 1.B.13), so the case is applicable for the Injury Profile. In describing the clinical course after his arrival at the hospital, the report states "during the next few hours the patient's mental status improved, and his dyspnea and cyanosis resolved. Five hours after the accident, the patient was completely oriented and lucid."[431] The report then lists a few mild symptoms that persisted at 5 hours post-accident. On the basis of this single patient (admittedly, not ideal), the H_2S Severe Injury Profile models recovery from Injury Severity Level 2 to Injury Severity Level 1 at 5 hours.

For the total time to recovery, Burnett et al.'s review of 221 cases proves useful. They note that 74% of the cases (164) lost consciousness, but only 14 of them "were sufficiently ill to require support in an intensive care unit."[432] It seems that the remaining 150 cases were "Severe" but not "Very Severe." Since no drugs that should be expected to shorten the clinical course were given, the time to hospital discharge of those 150 Severe cases is useful for the Injury Profile. The report states that the *average* hospital stay (excluding those patients in the ICU) was 2 days.[433] Thus, the H_2S Severe Injury Profile includes recovery from Injury Severity Level 1 to Injury Severity Level 0 at 2 days (2,880 minutes).

For the Very Severe Injury Profile, the symptoms involve nearly instant unconsciousness and *apnea*. It is clear in the literature that apnea is a primary cause of death.[434] Since recovery from complete apnea typically requires respiratory support (such as artificial ventilation)[435] and the Injury Profiles do not consider medical treatment, the

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429 P. Jappinen and R. Tenhunen, "Hydrogen Sulphide Poisoning: Blood Sulphide Concentration and Changes in Haem Metabolism," *British Journal of Industrial Medicine* 47, no. 4 (1990): 283–285.

430 Hsu, Li, and Lin, "Acute Hydrogen Sulfide Poisoning Treated with Hyperbaric Oxygen," 215.

431 Stine, Slosberg, and Beacham, "Hydrogen Sulfide Intoxication," 756.

432 Burnett et al., "Hydrogen Sulfide Poisoning: Review," 1280.

433 Ibid., 1278.

434 National Research Council, "Hydrogen Sulfide,"177–179; Stine, Slosberg, and Beacham, "Hydrogen Sulfide Intoxication," 757; Burnett et al., "Hydrogen Sulfide Poisoning: Review," 1280.

435 Sayers et al., *Investigation of Toxic Gases*, 61–62; Beauchamp et al., "A Critical Review of the Literature on Hydrogen Sulfide Toxicity," 38; Hsu, Li, and Lin, "Acute Hydrogen Sulfide

Very Severe Injury Profile ends at 15 minutes, when the casualty will be modeled to become KIA (consistent with the default value of $T_{death\text{-}CN\text{-}SL4}$).

Table 114 summarizes the H_2S Injury Profiles.

Table 114. Inhaled H_2S Injury Profiles

Time Point (min)	H_2S Mild	H_2S Moderate	H_2S Severe	H_2S Very Severe
1	1	2	3	4
10	1	1	2	4
15	1	1	2	4[a]
60	0	1	2	
120	0	0	2	
300	0	0	1	
2880	0	0	0	

[a] Death is modeled to occur at this point, based on the default value of the parameter $T_{death\text{-}CN\text{-}SL4}$ in *AMedP-7.5*.

Medical Treatment (*AMedP-7.5 Table 4-47*)

13. Efficacy of Medical Treatment

Medical treatment of H_2S poisoning involves supportive care and possibly antidotes. There is debate over whether certain cyanide antidotes are effective for H_2S poisoning. Even if antidotes are part of national doctrine, no self-aid or buddy aid is available for battlefield administration of the antidotes. The nearest location at which a solder could receive supportive care, and antidotes if part of national doctrine, would be a Role 1 MTF.

There is much debate over whether amyl nitrite and sodium nitrite are effective as antidotes for H_2S poisoning.[436] The theory is that nitrites cause the formation of

Poisoning Treated with Hyperbaric Oxygen," 215; Daniel S. Gabbay, Francis De Roos, and Jeanmarie Perrone, "Twenty-Foot Fall Averts Fatality from Massive Hydrogen Sulfide Exposure," *Journal of Emergency Medicine* 20, no. 2 (2001): 141–144.

436 Agency for Toxic Substances and Disease Registry, *Management Guidelines for Hydrogen Sulfide* (*H_2S*) (Atlanta, GA: ATSDR, 2011); Guidotti, "Hydrogen Sulphide"; Reiffenstein, Hulbert, and Roth, "Toxicology of Hydrogen Sulfide"; Stine, Slosberg, and Beacham, "Hydrogen Sulfide Intoxication"; Jack W. Snyder et al., "Occupational Fatality and Persistent Neurological Sequelae after Mass Exposure to Hydrogen Sulfide," *American Journal of Emergency Medicine* 13, no. 2 (1995): 199–203; F. M. Andeau, C. Gnanaharan, and K. Davey, "Hydrogen Sulphide Poisoning Associated with Pelt Processing," *New Zealand Medical Journal* 98, no. 774 (1985): 145–147; C.-C. Huang and N.-S. Chu, "A Case of Acute Hydrogen Sulfide (H_2S) Intoxication Successfully Treated with Nitrites," *Journal of the Formosan Medical Association* 86, no. 9 (1987): 1018–1020; Daniel D. Whitcraft, Todd B. Bailey, and George B. Hart, "Hydrogen Sulfide Poisoning Treated with Hyperbaric Oxygen," *Journal of Emergency Medicine* 3, no. 1 (1985): 23–25; Martin J. Smilkstein et al., "Hyperbaric Oxygen Therapy for Severe Hydrogen Sulfide Poisoning," *Journal of Emergency Medicine* 3, no. 1 (1985): 27–30; Gregg Gerasimon et al., "Acute Hydrogen Sulfide Poisoning in a Dairy Farmer," *Clinical Toxicology* 45, no.4 (2007): 420–423.

methemoglobin, which has a higher affinity for H_2S than cytochrome *c* oxidase, and therefore selectively binds the poison, allowing cytochrome *c* oxidase to participate in cellular metabolism. This process is analogous to nitrites as antidotes for cyanide poisoning. But the window of opportunity for nitrites to be effective is shorter for H_2S than for cyanide.[437] One possible explanation is that sulfide does not bind as strongly to methemoglobin as cyanide.[438] Burnett et al., in summarizing their experience with 221 cases of H_2S poisoning, conclude, "there was no evidence that any particular benefit accrued from nitrite therapy."[439] They recommended instead that first aid personnel and physicians focus on respiratory and circulatory support. Thus, the treatment model does *not* include nitrites (or anything else) as antidotes for H_2S poisoning.

The remaining medical treatment option is supportive care—particularly, artificial respiration and circulatory support. For H_2S, we did not find any case reports that could allow an estimate of PF_{SC}, because there were no cases in which the dose was known with reasonable certainty. However, since the primary mechanism of poisoning and supportive care given to casualties of H_2S and cyanide poisoning are the same, it seems reasonable to apply PF_{SC} from the AC model—a protection factor of 2—to the H_2S model. This protection factor is implemented by modeling survival for Very Severe casualties whose Effective CBRN Challenge is less than two times the LCt_{50}, or less than 6400 mg-min/m^3. The modeled time to RTD for survivors and time to DOW for non-survivors are discussed in the next subsection.

14. MTOR Table

Table 115 is the MTOR table for H_2S casualties. The table is derived from the Injury Profiles and RTD and DOW estimates from clinical case reports. Medical treatment comprises supportive care, and its effect in terms of the model is that if provided quickly enough, it can prevent death in some Very Severe casualties (those with Effective CBRN Challenge less than 6400 mg-min/m^3). Although one might expect that medical treatment could result in faster RTD for Severe, Moderate, or Mild casualties, we found no such evidence in the literature. We attribute this finding to the rapid recovery that occurs as long as the victim is not completely apneic.

In the discussions that follow, which explain Table 115, the potential for administrative declaration of asymptomatic "casualties" or delay of RTD for additional monitoring is ignored, consistent with the limitation discussed in Section 0.

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437 Agency for Toxic Substances and Disease Registry, *Management Guidelines for Hydrogen Sulfide* (*H_2S*), 12; Gerasimon et al., "Acute Hydrogen Sulfide Poisoning," 420; Reiffenstein, Hulbert, and Roth, "Toxicology of Hydrogen Sulfide," 129; Snyder et al., "Occupational Fatality and Persistent Neurological Sequelae," 201.

438 Roger P. Smith and R. E. Gosselin, "On the Mechanism of Sulfide Inactivation by Methemoglobin," *Toxicology and Applied Pharmacology* 8, no. 1 (1966): 159–172.

439 Burnett et al., "Hydrogen Sulfide Poisoning: Review," 1280.

Table 115. H_2S Medical Treatment Outcome Reporting

Injury Profile	DOW[a]	CONV[a]	RTD[a]
H_2S Mild	0%	0%	Day 2: 100%
H_2S Moderate	0%	0%	Day 2: 100%
H_2S Severe	0%	0%	Day 3: 100%
If casualties receive supportive care:			
H_2S Very Severe, $X^{eff}_{H2S,ih}$[b] < 6,400[c]	0%	0%	Day 21: 100%
H_2S Very Severe, $X^{eff}_{H2S,ih}$[b] ≥ 6,400[c]	Day 21: 100%	0%	0%

[a] Reported values indicate the fraction that changes status on a given day; they are not cumulative.

[b] $X^{eff}_{H2S,ih}$ is the Effective CBRN Challenge (dosage) of inhaled H_2S.

[c] These rows are only used if the user changes the value(s) of $T_{death\text{-}CN\text{-}SL4}$ and/or T_{MTF} such that $T_{MTF} \leq T_{death\text{-}CN\text{-}SL4}$, which will allow casualties in the Very Severe cohort to survive long enough to reach medical treatment. Note that if this change is *not* made, the casualties in the Very Severe cohort will be KIA, so they are not included in the MTOR table.

Based solely on the Injury Profiles, casualties in the H_2S Mild and Moderate cohorts will recover sufficiently to RTD on Day 1, so they are reported as RTD on Day 2 in the MTOR. Likewise, RTD for the Severe cohort is Day 3, based on the Injury Profile showing full recovery at the end of Day 2.

The remaining question is, if Very Severe casualties do reach the MTF, when can the survivors RTD and when do the non-survivors DOW? Burnett et al. reported that 14 of their cases required support in an ICU, and that the average stay in the ICU was 21 days (additional details were not available). Although the report states that four patients died after admission and that these four were presumably in the ICU, it is not clear whether the average ICU stay was different for survivors and non-survivors. Given the lack of other information from Burnett et al. or other sources, we chose to model both non-survivor DOW and survivor RTD at 21 days.

As a final note, although H_2S also causes irritation symptoms, the best case report summary we found (Burnett et al.) focuses primarily on respiratory and neurological symptoms, which are a result of the systemic action of H_2S. Irritation symptoms are noted but not discussed very much. Apparently, irritation symptoms have little impact on the time until death or full recovery.

1.14. Radiological Assumptions and Limitation, Nuclear Assumptions and Limitation, and Threshold Lethal Dose and Time to Death (*AMedP-7.5 Sections 4.3.1, 4.4.1, and 4.3.4*)

Radiological Agent Assumptions and Limitation (*AMedP-7.5 Section 4.3.1*)

Assumption: Individuals will clean their exposed skin and dust off their clothing and materiel after exiting the radiation area.

This assumption reflects typical military training and is reflected in the equations by the fact that dose does not continue to accumulate for long periods after the contamination is spread.

Assumption: Human response is independent of the source of exposure. For example, whole-body radiation Injury Profiles for radiological incidents are identical to those used for whole-body radiation under the nuclear effects models.

That is, a gamma ray, for example, is a gamma ray, regardless of its origin.

Assumption: Human response due to whole-body radiation dose and cutaneous radiation dose are independent of one another—the effects of each challenge type are modeled separately, and are only combined via a Composite Injury Profile.

This assumption is necessary for the purpose of modeling, even though we believe there would be some interaction (and potential synergy) between the two injuries, because there are insufficient data to create a combined model.

Assumption: For the purpose of estimating time to death due to whole-body radiation, each icon's dose rate is equal to the icon's total whole-body dose divided by the time during which the dose accumulated.

This assumption is necessary because of limited data on the relationship between instantaneous time-varying dose rate and time to death.

Limitation: Dose protraction—a sufficiently low dose rate such that some physiological recovery occurs simultaneously with the challenge—is only included as it pertains to determining whether a casualty will die; the Injury Profiles do not account for dose protraction.

This limitation is a result of limited data on the relationship between dose rate and severity of injury—a possible result of this limitation is an overestimate of the severity of some injuries. The relationship between dose rate and probability of fatality is included because sufficient data are available.

Nuclear Effects Assumptions and Limitations (*AMedP-7.5 Section 4.4.1*)

Assumption: Human response is independent of the source of exposure. For example, whole-body radiation Injury Profiles for radiological incidents

are identical to those used for whole body radiation under the nuclear effects models.

That is, a gamma ray, for example, is a gamma ray, regardless of its origin.

Assumption: The entire challenge occurs immediately following the detonation (consistent with fallout being modeled separately, as described in Section 4.3.3).

The prompt nuclear effects (initial radiation, blast, and thermal fluence) truly do occur nearly instantaneously. This assumption indicates that the model treats them as literally instantaneous—a small and insignificant distinction.

Limitation: The combined effects of prompt nuclear injuries are not considered; Composite Injury Profiles are not used, and initial radiation, blast, and burn injuries are considered separately.

There are many possible combinations of radiation, blast, and thermal doses and ranges, and very little data available on combined injuries. Thus, creating a model of such injuries is not feasible, and each injury is therefore treated separately, as if there were no synergy between the different types of injury.[440]

Threshold Lethal Dose and Time to Death (*AMedP-7.5 Section 4.3.4*)

Threshold Lethal Dose

For a given total whole-body radiation dose, the slower that dose is received (i.e., the lower the dose rate) the more time the body's natural healing mechanisms have to combat its physiological effects. The result is that a lower dose rate will reduce the expected lethality of the total radiation dose. McClellan, Crary, and Oldson published data on the probability of mortality as a function of *protracted* radiation doses, where protraction refers to a relatively low dose rate as compared to the nearly instantaneous accumulation of radiation dose resulting from a nuclear detonation.[441] Data presented by McClellan, Crary, and Oldson, reproduced in the first two columns of Table 116, are derived from the Radiation-Induced Performance Decrement (RIPD) software developed by the Defense Nuclear Agency in the 1990s. The rightmost two columns of Table 116 are plotted in Figure 5 as blue diamonds. A fit line, described by *AMedP-7.5* Equation 4-32, is plotted in red. The fit line plateaus at approximately 1.0, as it should, and follows what appears to be a reasonable trajectory as it goes beyond the range of the underlying data.

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440 Although an earlier IDA document proposed a model for combined effects, the proposed model was inconsistent with the untreated models already accepted in *AMedP-8*(*C*), so it was not adopted.

441 Gene E. McClellan, David J. Crary, and Darren R. Oldson, *Approximating the Probability of Mortality Due to Protracted Radiation Exposures*, DTRA-TR-16-054 (Fort Belvoir, VA: Defense Threat Reduction Agency, June 2016), 11, Table 1.

The functional form of *AMedP-7.5* Equation 4-32 was derived using open-source curve-fitting software (available at https://github.com/zunzun/pyeq2) that fits a large number of linear and nonlinear functions to a given dataset using a genetic algorithm. It then ranks the fits, using a measure such as Akaike Information Criteria (AIC), and reports these results back to the user. We considered the top three ranked functions returned by the software, but found of that of the three, only the form we chose gave reasonable results when extrapolating outside the dose rate range of the fitted data (specifically, to lower dose rates, which is an important consideration since lower dose rates are certainly possible).

Note that dose rate in Table 116 and in *AMedP-7.5* Equation 4-32 is treated as a constant. Thus, *AMedP-7.5* Equation 4-32 is best applied when the dose rate is approximately constant, such as in the contamination area produced by an RDD with a long-lived radioisotope or in a fallout area more than a few hours old.

A second caveat for the use of *AMedP-7.5* Equation 4-32 is that ideally, dose protraction should be accounted for separately for cloudshine, groundshine, and inhalation dose. That is, the dose rate for each route of exposure should be separately calculated based on its own specific duration. The McClellan, Crary, and Oldson model does not allow for this, however. Therefore, users should be aware that the duration of groundshine will typically be longest, and thus if cloudshine is a large component of the overall dose, *AMedP-7.5* will estimate a threshold dose higher than it would be if the rapidity of cloudshine dose accumulation were properly accounted for.

Table 116. Data from McClellan, Crary, and Oldson Used to Generate *AMedP-7.5* Equation 4-32

Exposure Duration (hr)	LD_{50} (Gy)	Log (Dose Rate [Gy/hr])	LD_{50} Dose Ratio ($LD_{50@0.02}/LD_{50}$)
0.02	4.095	2.31	1.000
0.1	4.134	1.62	0.991
0.25	4.204	1.23	0.974
0.5	4.312	0.94	0.950
1	4.497	0.65	0.911
2	4.776	0.38	0.857
4	5.16	0.11	0.794
8	5.557	–0.16	0.737
16	5.958	–0.43	0.687
32	6.415	–0.70	0.638
48	6.77	–0.85	0.605
72	7.26	–1.00	0.564
120	8.233	–1.16	0.497
168	9.247	–1.26	0.443

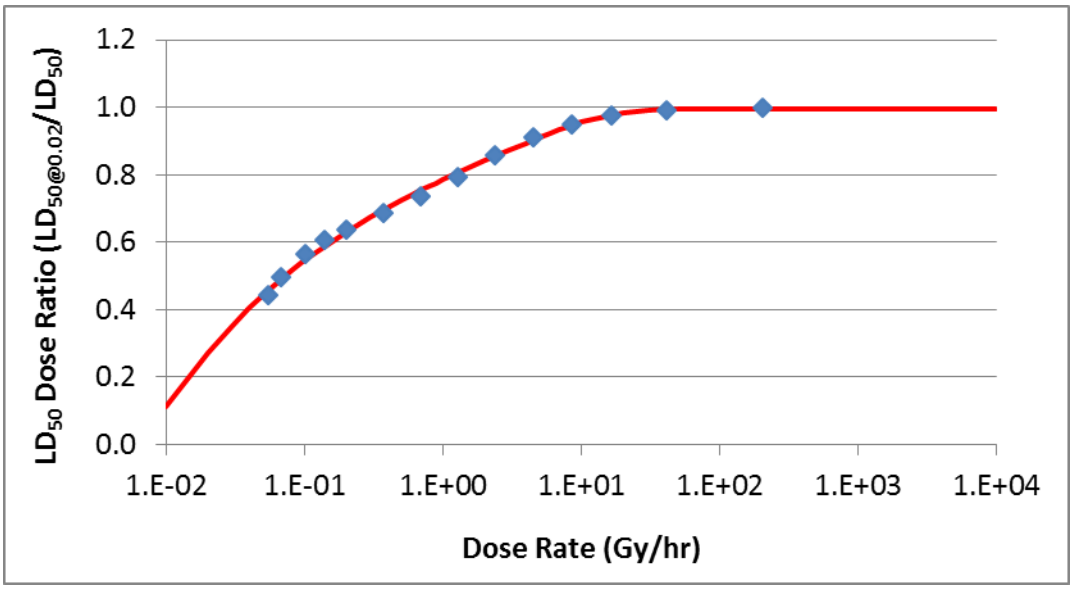

Figure 5. Data and Fit Line for Data Presented by McClellan, Crary, and Oldson

The whole-body radiation LD_{50}s[442] for instantaneous challenges listed in *AMedP-7.5* Table 4-48 are used as input to *AMedP-7.5* Equation 4-32. The doses listed in *AMedP-7.5*

442 Although these values are usually referred to as $LD_{50/60}$, with the 60 indicating death within 60 days, they will be referred to simply as LD_{50} here for consistency with *AMedP-7.5*.

are the free-in-air dose, not the personal or tissue dose, because the free-in-air dose is what is measurable and what is predicted by hazard-prediction models. A well-accepted estimate for the untreated personal dose LD_{50} is 3.5 Gy.[443] According to IAEA-TECDOC-1564, the averaged conversion coefficient from air kerma to personal dose equivalents for radiation fields of quality RQR4 and RQR9 are 1.098 and 1.485, respectively.[444] Anno et al. have estimated the conversion factor as 1.5 for midline tissue dose and as 1.41 for bone marrow.[445] These estimates cover the approximate range of factors given in ICRP 116.[446] Since it is necessary for the purpose of *AMedP-7.5* to have a single factor, we simply used the value in the middle of the approximate range—the range appears to be about 1.1 to 1.5, so we used 1.3. Multiplying 3.5 Gy by 1.3 gives 4.55 Gy, which we rounded to 4.5 Gy for use in *AMedP-7.5*.

Note that the estimated LD_{50} of 4.5 Gy differs slightly from Anno et al., who specified an $LD_{50/30}$ of 4.1 Gy with 95% confidence bounds of 2.55–5.50 Gy. [447] The Anno et al. value is also used in Joint Publication 3-11.[448] We used 4.5 Gy because it is within the error bounds of the other estimate and is more consistent with the time-to-death data presented in the next subsection.

The second row of *AMedP-7.5* Table 4-48 is for "medical treatment excluding G-CSF," which means supportive care only. Several sources have estimated a factor by which the LD_{50} increases as a result of supportive care (a dose reduction factor, or DRF). Based on a comparison of Chernobyl versus Nagasaki, Anno et al. estimated a DRF of 2.0.[449] There are several problems with the Chernobyl/Nagasaki dataset, including differences in age, sex, initial population health, and dose distributions. Based on canine data that were much better controlled to avoid confounding influences, MacVittie et al. estimated a DRF for the $LD_{50/30}$ of either 1.3 or 1.21, depending on the radiation source.[450] Other studies

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443 Ronald E. Goans and Daniel F. Flynn, "Acute Radiation Syndrome in Humans," in *Medical Consequences of Radiological and Nuclear Weapons*, ed. Anthony B. Mickelson, Textbooks of Military Medicine (Washington, DC: OTSG, Department of the Army, 2012), 25.

444 International Atomic Energy Agency, *Intercomparison of Personal Dose Equivalent Measurements by Active Personal Dosimeters*, IAEA-TECDOC-1564 (Vienna: IAEA, November 2007), 13.

445 George H. Anno et al., "Dose Response Relationships for Acute Ionizing-Radiation Lethality," *Health Physics* 84 (2003): 567.

446 N. Petoussi-Henss et al., *Conversion Coefficients for Radiological Protection Quantities for External Radiation Exposures*, ICRP Publication 116 (Ottowa, Ontario: ICRP, 2010).

447 Anno et al., "Dose Response Relationships," 573.

448 Joint Publication 3-11, *Operations in Chemical, Biological, Radiological, and Nuclear Environments* (Washington, DC: U.S. GPO, 4 October 2013).

449 Anno et al., "Dose Response Relationships," 565–575.

450 MacVittie et al., "The Relative Biological Effectiveness of Mixed Fission-Neutron-γ Radiation on the Hematopoietic Syndrome in the Canine: Effect of Therapy on Survival," *Radiation Research* 128 (1991): S29–36.

based on NHPs have estimated DRFs of 1.13 ($LD_{50/60}$)[451] and 1.45 ($LD_{50/30}$)[452] Considering the quality and quantity of the data from NHPs, canines, and humans, IDA has previously estimated the DRF for supportive care in humans to be 1.5 at the LD_{50}.[453] Multiplying 4.5 Gy by 1.5 gives the value of 6.75 Gy that is given in *AMedP-7.5* Table 4-48.

The *AMedP-7.5* Table 4-48 LD_{50} for treatment including G-CSF is based on the DRF of 1.88 determined by MacVittie, Farese, and Jackson. Multiplying 4.5 Gy by 1.88 gives 8.46 Gy, which we rounded to 8.5 Gy for *AMedP-7.5*.[454]

Time to Death

Although several different approaches for estimating time to death from whole-body radiation have been proposed in the past, *AMedP-8*(*C*) used data extracted from Figure C-21 of the document *Personnel Risk and Casualty Criteria for Nuclear Weapons Effects*, also known as the *PRCC*.[455] The *PRCC* figure is reproduced below as Figure 6—the data used in both *AMedP-8*(*C*) and now in *AMedP-7.5* were extracted from the diagonal line marking the "death" region.

451 A. M. Farese et al., "A Nonhuman Primate Model of the Hematopoietic Acute Radiation Syndrome Plus Medical Management," *Health Physics* 103 (2012): 367–382.

452 Calculated from Farese et al., "Pegfilgrastim Administered in an Abbreviated Schedule, Significantly Improved Neutrophil Recovery after High-Dose Radiation-Induced Myelosuppression in Rhesus Macaques," *Radiation Research* 178, No. 5 (2012): 403–413, by taking the $LD_{50/30}$ with supportive care (7.18) and dividing it by the $LD_{50/30}$ without supportive care (4.93).

453 Katherine M. Sixt et al., *Research and Development Strategies for the Current and Future Treatment of Radiation Casualties*, IDA Paper P-5160 (Alexandria, VA: IDA, September 2014), B-3.

454 T. J. MacVittie, A. M. Farese, W. Jackson III, "Defining the Full Therapeutic Potential of Recombinant Growth Factors in the Post Radiation Accident Environment: The Effect of Supportive Care Plus Administration of G-CSF," *Health Physics* 89 (2005): 546–55.

455 U.S. Department of the Army, *Personnel Risk and Casualty Criteria*.

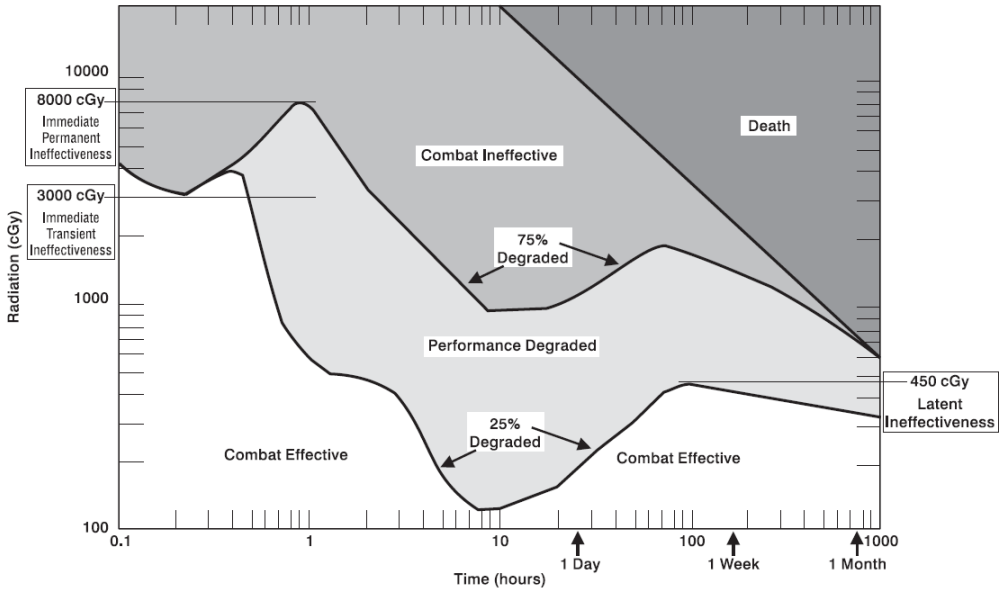

Figure 6. Figure C-21 from the PRCC: "Expected Performance Response to Radiation"

The *AMedP-7.5* equation is different from that in *AMedP-8*(*C*) because the output is converted to units of days instead of hours, and the equation has been simplified. *AMedP-7.5* Equations 4-33 (RDD/fallout) and 4-35 (initial whole-body radiation) are both restricted to a dose less than 100 Gy because a dose greater than this threshold could result in an estimate of KIA due to the injury. Such rapid death has never been observed as a result of whole-body radiation exposure—allowing the methodology to estimate a whole-body radiation KIA would be extrapolating far beyond the supporting data.

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1.15. RDDs, Fallout, and Initial Whole-Body Radiation (Nuclear) (*AMedP-7.5 Sections 4.3.2, 4.3.3, 4.3.5, and 4.4.2*)

Introduction

The adverse consequences to human health of radioactivity and ionizing radiation were first recognized shortly after their discovery in the late 19th century.[456] The intentional exposure of individuals to radiation may occur in a number of ways, including the deliberate use of ionizing radiation as a weapon and indirectly as a result of radioactive fallout following detonation of a nuclear device. One such tool for accomplishing the former task is a radiological dispersal device (RDD). Detonation of a nuclear weapon will directly produce radiation, and may also produce fallout, which includes the fission products, unfissioned nuclear material, and weapon residues, as well as soil that has been vaporized by the heat of the fireball. Radioactive fallout deposited on the ground may pose a hazard from external gamma and beta radiation exposure even to reasonably protected troops operating in the contaminated area.

Note that *AMedP-7.5* Equations 4-23 to 4-30 (RDD), Equation 4-31 (fallout), and Equation 4-34 (nuclear initial whole-body radiation) simply sum the various components of each type of dose; no further explanation is warranted in this chapter.

RDD Assumptions, Limitations, and Constraint (*AMedP-7.5 Section 4.3.2.2*)

> **Assumption**: The activity deposited on the ground at the icon's location is equal to the activity deposited on the skin of each individual in the icon.

This assumption is made because most transport and dispersion models do not include individuals in the simulation, and ground deposition is the most relevant related information that is typically calculated by such models.

> **Assumption**: For calculations of dose due to groundshine, the activity concentration at the icon's location for the time period of interest is uniformly extended to infinity in all directions.

This assumption, which is made to simplify the calculation of dose, has the effect of artificially increasing the calculated dose to a small extent.

> **Assumption**: For the purpose of deriving the dose conversion factors in Table 3-1, absorbed dose (in units of gray) is equal to dose equivalent (in units of Sievert).

An alternate statement of this assumption is that neutron and gamma radiation are assumed to have a relative biological effectiveness (RBE) of 1. In reality, RBE depends on

456 Merril Eisenbud and Thomas Gesell, *Environmental Radioactivity from Natural, Industrial, and Military Sources*, 4th ed. (San Diego: Academic Press, 1997), 4.

tissue type, and there is controversy about specific values for neutron and gamma radiation. This simplifying assumption avoids both those problems, but also may artificially reduce the calculated dose.

> **Assumption**: Cutaneous dose due to beta emitters contaminating the clothing is negligible (contamination of the skin is counted).

This assumption reflects the fact that clothing will absorb a significant portion of beta radiation.

> **Assumption**: The dose from inhalation of radiological particles is equal to the 30-day committed effective dose equivalent and is combined with the cloudshine and groundshine doses to determine an overall whole-body dose.

This assumption—that the dose is equal to the 30-day committed effective dose equivalent—is made because this methodology is intended for operational planning, not estimation of longer term effects like cancer. The inhalation dose is combined with the cloudshine and groundshine doses because this methodology only deals with whole-body and cutaneous radiation dose—effects on other parts of the body (such as the lungs) are not individually modeled. For an RDD containing primarily alpha radiation emitting particles, this assumption will result in a significant underestimate of injury.

> **Limitation**: Conventional casualties (i.e., from high explosives and fragmentation) that might occur as part of a RDD incident are ignored.

The purpose of this methodology is not to estimate conventional casualties, so this aspect of a potential RDD is ignored. If a user wishes to account for the conventional casualties from an RDD, other established national capabilities for estimating such effects should be used.

> **Limitation**: Gamma radiation due to skin contamination is ignored because it is typically only a few percent of the beta radiation dose.

This limitation, which simplifies the calculation of cutaneous dose, will cause a slight artificial reduction in the calculated dose.

> **Constraint**: Because the user is forced to choose either a gamma radiation protection factor *or* a beta radiation protection factor for each isotope, that protection factor is applied to all radiation emitted by that isotope.

This constraint reflects a limitation of the methodology. Since most isotopes primarily emit one type of radiation, the error introduced into dose calculations will be minimal. This constraint could cause the dose to be slightly artificially increased or decreased, depending on the specific scenario and the user's choice of protection factor.

Fallout Assumptions, Limitations, and Constraint (*AMedP-7.5 Section 4.3.3.2*)

Assumption: Icons enter the radiation area only after all fallout has deposited on the ground.

This assumption is necessary because most hazard-prediction models cannot account for the rapidly changing dose and dose rate as a function of the age of the fallout cloud.

Assumption: The deposition concentration on the skin (caused by resuspension) is equal to the ground concentration at the icon's location.

This assumption is made because most transport and dispersion models do not include individuals in the simulation, and ground deposition is the most relevant related information that is typically calculated by such models.

Limitation: Gamma radiation due to skin contamination is ignored because it is typically only a few percent of the beta radiation dose.[457]

This limitation, which simplifies the calculation of cutaneous dose, will cause a slight artificial reduction in the calculated dose.

Limitation: Isotope-specific dose calculations are not performed for fallout because most hazard-prediction models do not specify the distribution of radioisotopes in fallout.

This limitation is self-explanatory.

Constraint: Only radiation from groundshine and skin contamination are considered.

This constraint is related to the first assumption. Since the fallout cloud is assumed to have settled, there will be no cloudshine dose.

Nuclear Initial Whole-Body Radiation Assumption (*AMedP-7.5 Section 4.4.2.2*)

Assumption: The relative biological effectiveness (RBE) for neutron/gamma radiation is 1.

In reality, RBE depends on tissue type, and there is controversy around specific values for neutron and gamma radiation. This simplifying assumption avoids both those problems, but also may artificially reduce the calculated dose.

Physiological Effects (*AMedP-7.5 Tables 4-49 and 4-52*)

Regardless of whether it originates from a RDD, fallout, or the initial radiation from a nuclear detonation, ionizing radiation causes injury to a number of physiological systems

457 International Atomic Energy Agency (IAEA), *Generic Procedures for Assessment and Response During a Radiological Emergency*, IAEA-TECDOC-1162 (Vienna: IAEA, 2000), 104.

through the deposition of energy in the organ tissues—both electromagnetic (e.g., X-rays and gamma rays) and particulate radiation (e.g., beta particles, alpha particles, and neutrons). The deposition of energy produces free radicals that in turn interact with the body chemistry, causing damage to the cells and cellular material.[458] The resulting damage is a function of a number of factors, including the dose, the time post-exposure, and the sensitivity of the cellular material, among others.[459] Thus, the higher the dose, the greater the resulting damage, the worse the anticipated injury severity, and the shorter the latent period before the injury manifests as symptoms, otherwise known as acute radiation syndrome (ARS).[460]

ARS is actually a combination of syndromes affecting multiple physiological systems, including the hematopoietic (HP), gastrointestinal (GI), and cerebrovascular (CV) systems.[461] Damage to a fourth organ system, the skin, may also result in casualties, if sufficient quantities of beta-emitting radioisotopes remain in contact with the skin for a long enough period of time. In each syndrome, the exposed individual would be expected to progress through four possible stages—prodromal, latent, manifest illness, and possible recovery. The length of each stage in a particular physiological syndrome, as well as the severity of injury in each stage, is a function of the dose received by the exposed individual.

In the hematopoietic syndrome, the deposited energy targets stem cells in the bone marrow. "A dose-dependent suppression of bone marrow may lead to marrow atrophy and pancytopenia. Prompt radiation doses of about 1–8 Gy may cause significant damage to the bone marrow."[462] A brief prodromal period—days—may have symptoms including nausea, vomiting, anorexia, diarrhea, fatigue, and weakness. At lower doses, the latent period may last for weeks; at higher doses, however, the latent period may be days or shorter. The manifest illness stage may include moderate bleeding, fever, and ulceration; at the highest doses, platelet loss, anemia, hemorrhage, and infection as a result of pancytopenia from the bone marrow suppression may cause lethality.[463]

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458 Leonard A. Alt, C. Douglas Forcino, and Richard I. Walker, "Nuclear Events and Their Consequences," in *Medical Consequences of Nuclear Warfare,* ed. Richard I. Walker and T. Jan Cerveny, Textbook of Military Medicine (Falls Church, VA: Department of the Army, Office of the Surgeon General, Borden Institute, 1989), 13–14.

459 Eric J. Hall, *Radiobiology for the Radiologist*, 5th ed. (Philadelphia, PA: Lippincott Williams &Wilkins, 2000), 17.

460 Ibid.

461 Donald Pizzarello and Richard Witcofski, *Medical Radiation Biology*, 2nd ed. (Philadelphia, PA: Lea and Febiger, 1982), 136.

462 T. Jan Cerveny, Thomas J. MacVittie, and Robert W. Young, "Acute Radiation Syndrome in Humans," in *Medical Consequences of Nuclear Warfare* ed. Richard I. Walker and T. Jan Cerveny, Textbook of Military Medicine (Falls Church, VA: Department of the Army, Office of the Surgeon General, Borden Institute, 1989), 19.

463 Anno et al., "Symptomatology of Acute Radiation Effects;" George H. Anno, D. B. Wilson, and S. J. Baum, *Severity Levels and Symptom Complexes for Acute Radiation Sickness: Description and Quantification*, PSR Report 1597 (Los Angeles, CA: Pacific Sierra Research

The gastrointestinal syndrome follows a similar, but shortened, course of illness. The prodromal stage may include nausea, vomiting, diarrhea, cramps, and resulting fatigue and weakness. The shorter latent period—days—may be the result of damage to mucosal lining. In a healthy individual the mucosal lining, which regenerates every 3–5 days, creates a barrier to the escape of mucosal flora and other materials from the gastrointestinal system; following radiation exposure, the mucosal lining sheds but does not regenerate. As a result, a potential pathway is opened from mucosal flora and other materials to escape the gastrointestinal system and enter the circulatory system. Further, this shedding of the mucosal layer alters the body's ability to correctly absorb necessary nutrients. The manifest illness, therefore, will likely include symptoms similar to those in the prodromal period but may also include malnutrition, mucosal ulceration, and dehydration. At higher doses, sepsis, acute renal failure, anemia, and cardiovascular system collapse are also possible.[464]

The cardiovascular syndrome course of illness is more difficult to describe. Typically, this syndrome is observed in individuals with doses in excess of 20–30 Gy.[465] Although the prodromal and latent period manifest similarly to the other syndromes, these symptoms appear quickly and may be accompanied by confusion and dizziness. The latent period, if it occurs at all, may be short—hours. The manifest illness stage includes vomiting, diarrhea, cardiac and respiratory distress, and central nervous system failure.[466] Doses high enough to induce the cerebrovascular syndrome will result in death within hours of exposure. Incapacitation may result within minutes. However, only very unusual circumstances would lead to acute doses from a radiological agent capable of inducing the cerebrovascular syndrome. Examples of lethal exposures resulting in cerebrovascular syndrome have historically involved very sudden, short-duration events, such as criticality accidents.[467]

If the lungs receive a large dose at a high dose rate, a pulmonary syndrome may also develop. Because an external dose that might produce this effect will also induce the hematopoietic syndrome, the pulmonary syndrome and its associated symptoms are

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Corporation, 30 November 1985), 6–17; and Cerveny, MacVittie, and Young, "Acute Radiation Syndrome in Humans," 19–20.

464 Anno et al., "Symptomatology of Acute Radiation Effects," 827–833; Anno, Wilson, and Baum, *Severity Levels and Symptom Complexes*, 6–17; Cerveny, MacVittie, and Young, "Acute Radiation Syndrome in Humans,"19–20; and Hall, *Radiobiology for the Radiologist*, 126–128.

465 Cardiovascular symptoms may occur at lower doses. Studies do not appear consistent regarding whether cardiovascular distress resulting from hypovolemia, which can occur at doses as low a 7.5 Gy, are considered part of the cardiovascular syndrome. Robert W. Young, "Acute Radiation Syndrome," in *Military Radiobiology*, ed. James J. Conklin and Richard I. Walker (San Diego, CA: Academic Press, Inc., 1990), 167–171.

466 Cerveny, MacVittie, and Young, "Acute Radiation Syndrome in Humans," 20–21; and Anno et al.,"Symptomatology of Acute Radiation Effects," 827–833.

467 Hall, *Radiobiology for the Radiologist*, 126.

difficult to differentiate from hematopoietic syndrome symptoms.[468] Finally, because there are limited data that specifically address the pulmonary syndrome, it will not be examined further.

The physiological effects of skin exposure to beta emitters are highly dose dependent. Injury will likely not manifest for a week or more, except in the highest dose ranges. Redness; blisters; and a sensation of heat, edema, ulceration, and pain may occur once symptoms begin.[469] A total body skin exposure at levels capable of producing such symptoms would likely be fatal; partial exposures at such levels may require amputation of the affected area.

For the purposes of the *AMedP-7.5* methodology, external exposures to gamma radiation from a radiological event and exposure from inhaled radioactive material are treated as whole-body exposure events. External exposure from beta particles is treated as a dose to skin only.

Relative to the nuclear bomb scenario, the ionizing radiation dose in the RDD or fallout scenario is delivered over a longer, but finite, period of time. The time period of minutes to hours, however, is considered short enough to treat the external radiation as effectively instantaneous. The role of dose rate is not be taken into account when determining the potential for acute response, with the exception of its employment in estimating the probability of death (see Section 0).

Table 90 summarizes the preceding qualitative descriptions in a format amenable to use in *AMedP-7.5* and for the analysis presented in this chapter. Consistent with the definition of Injury Profile, the symptom sets are clinically differentiable.

Dose Ranges (*AMedP-7.5 Tables 4-49 and 4-52*)

Dose ranges were selected to represent clinically differentiable injury progressions as a function of dose. The ranges are shown in Table 117 and Table 118. Note that the symptom descriptions in Table 117 and Table 118 are derived from Section 0 of this chapter.

Table 117. Cutaneous Radiation Dose Ranges

Dose Range (Gy)	Set of Symptoms
<2	No observable injury
2 – <15	12 hours to 5 weeks post exposure: erythema, slight edema, possible increased pigmentation; 6 to 7 weeks post exposure: dry desquamation

468 Nuclear Regulatory Commission, *Probabilistic Accident Uncertainty Consequence Analysis*, NUREG/CR-6545 (Brussels-Luxembourg: European Commission, 1997).

469 Centers for Disease Control and Prevention (CDC), “Cutaneous Radiation Injury (CRI): Fact Sheet for Physicians,” http://emergency.cdc.gov/radiation/criphysicianfactsheet.asp, last updated December 10, 2015.

15 – <40	Immediate itching; 1 to 3 weeks post exposure: erythema, edema; 5 to 6 weeks post exposure: subcutaneous tissue edema, blisters, moist desquamation; late effects (>10 weeks)
40 – <550	Immediate pain, tingling for 1 to 2 days; 1 to 2 weeks post exposure: erythema, blisters, edema, pigmentation, erosions, ulceration, severe pain; severe late effects (>10 weeks)
≥550	Immediate pain, tingling, swelling; 1 to 4 days post exposure: blisters, early ischemia, substantial pain; tissue necrosis within 2 weeks, substantial pain

Table 118. Whole-Body Radiation Dose Ranges

Dose Range (Gy)	Set of Symptoms
<1.25	No observable injury
1.25 – <3	A slight decrease in white blood cell and platelet count with possible beginning symptoms of bone marrow damage; survival is greater than 90% unless there are other injuries
3 – <4.5	Moderate to severe bone marrow damage occurs; lethality ranges from $LD_{5/60}$ to $LD_{50/60}$; these patients require greater than 30 days recovery, but other injuries would increase the injury severity and likelihood of death
4.5 – <8.3	Severe bone marrow damage occurs; lethality ranges from $LD_{50/60}$ to $LD_{99/60}$; death occurs within 3.5 to 6 weeks with the radiation injury alone but is accelerated with other injuries; with other injuries death may occur within 2 weeks
≥8.3	Bone marrow pancytopenia and moderate intestinal damage occur, including diarrhea; death is expected within 2 to 3 weeks; with other injuries death may occur within 2 weeks; at higher doses, combined gastrointestinal and bone marrow damage occur with hypotension and death is expected within 1 to 2.5 weeks or, if other injuries are also present, within 6 days

The whole-body dose ranges in Table 118 are based on and condensed from the original Injury Severity Category tables included in the nuclear volume of *AMedP-8*(*A*).[470] In those tables, radiation injury severity was represented by eight dose ranges, but discussions with the NATO CBRN Medical Working Group (during the development of *AMedP-8*(*C*)) indicated that there were too many ranges. Moreover, these discussions suggested that dose ranges should ideally be clinically differentiable, and such was not clearly the case with the ranges found in *AMedP-8*(*A*).

To modify the whole-body dose ranges, we returned to the original Intermediate Dose Program (IDP) methodology, where signs and symptom progressions were prepared for four radiation doses—1.5 Gy, 3 Gy, 5 Gy, and 10 Gy.[471] These doses approximately correlated to the boundaries between the original *AMedP-8*(*A*), IDP, and *AMedP-6*(*C*) dose

470 NATO, *AMedP-8*(*A*) *Nuclear*, 3–9.

471 Levin, *Effect of Combined Injuries*, A-2–A-5.

ranges with one exception; the uppermost value—10 Gy—was approximately the midpoint of the sixth dose range. Higher doses were anticipated to cause similar lethality in shorter time periods; these dose ranges were therefore correlated into a single representative range. The "no observable effect" range was extended slightly to correspond to the *AMedP-6*(*C*) value of 0.75 Gy; documentation suggests that less than 5% of the population would be expected to suffer mild nausea at doses in this range.[472] Thus, this would seem to indicate that for most of the population, below this dose, there are no observable effects resulting from exposure. *AMedP-8*(*C*) used a dose range border of 5.3 Gy instead of the 4.5 Gy shown in Table 118; this was changed to 4.5 Gy for *AMedP-7.5* because it better aligns with the $LD_{50/60}$ (see Subsection 0).

The cutaneous radiation dose ranges in Table 117 are taken from the CDC.[473] *AMedP-8*(*A*) did not contain information related to cutaneous injury from skin contamination.

Injury Profiles(*AMedP-7.5 Tables 4-50 and 4-53*)

The Injury Profiles for initial whole-body radiation included in *AMedP-8*(*C*) were derived from symptom progressions, which show the severity level of symptoms in the physiological system in which they manifest (as opposed to the causative system) over time. The severity level of the Injury Profile at any given time point corresponds to the worst severity level experienced in any of the representative physiological systems at that time. The following sections explain the historical development of the symptom progressions and Injury Profiles for *AMedP-8*(*C*) and the slight changes to the Injury Profiles for *AMedP-7.5*.

Severity Levels and Symptoms

The first part of the process for *AMedP-8*(*C*) was deciding which physiological systems would be represented in the model. For external whole-body radiation, the DNA IDP methodology employed six sets of signs, symptoms, and systems to represent the injury progression: upper gastrointestinal, lower gastrointestinal, fatigability and weakness, infection and bleeding, hypotension, and fluid loss. These symptoms were represented on a severity scale of 1–5.[474]

In an effort to ensure clarity and consistency, the symptoms and systems for whole-body radiation were correlated to four representative physiological systems in which symptoms would be expected to *manifest* (not the *causative* system) following exposure to

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472 NATO, AMedP-6(C), *Volume I: NATO Handbook on the Medical Aspects of NBC Defensive Operations (Nuclear)* (Brussels: NATO, 2005); and U.S. Armed Forces Radiobiology Research Institute (AFRRI), *Medical Management of Radiological Casualties, Second Edition* (Bethesda, MD: AFRRI, April 2003), Table F-1.

473 CDC, "Cutaneous Radiation Injury (CRI)."

474 Levin, *Effect of Combined Injuries*, 5–6; Anno et al., *Performance on Infantry and Artillery Personnel*, 6; and Sheldon G. Levin, *Consolidated Human Response Nuclear Effects Model (CHRNEM)*, DNATR-93-45 (Alexandria, VA: Defense Nuclear Agency, 1993), 6–8.

nuclear radiation: cardiovascular, immune, lower gastrointestinal, and upper gastrointestinal. The cardiovascular system encompasses hypotension and bleeding and the immune system encompasses infection (fluid loss was not considered *AMedP-8*(*C*)). For cutaneous radiation, *AMedP-8*(*C*) only incorporated symptoms that manifest in the skin.

Contrary to the Injury Severity scale in Table 2, which is practically identical to the scale used in *AMedP-8*(*C*), the IDP severity levels for each of the six signs, symptoms, and systems were independent for each physiological system. For example, an upper gastrointestinal severity of 4, described as "vomited several times including the dry heaves; severely nauseated and will soon vomit again," while operationally challenging, was not, however, equivalent to an infection and bleeding (immune system) severity of 4, described as "delirious [due to fever]; overwhelming infections; cannot stop any bleeding," which could potentially kill the individual.

For *AMedP-8*(*C*) (and retained in *AMedP-7.5*), the symptom descriptions from IDP were aligned with the Table 2 severity scale so that, for instance, a Severity Level 2 injury to the upper gastrointestinal system consists of physiological symptoms of equal severity to those found in Severity Level 2 for the lower gastrointestinal system and Severity Level 2 for the cardiovascular system.. As a result, all represented physiological systems begin with a "no observable effect" level, but each system has only the number of Injury Severity Levels necessary to achieve the maximum injury severity at which symptoms for that physiological system occur. For example, since nobody is expected to die as a result of skin symptoms, there are no Severity Level 4 symptoms.

Table 119. Whole Body Radiation Symptoms and Severity Levels

Severity	Upper Gastrointestinal	Lower Gastrointestinal
0	No observable injury	No observable injury
1	Upset stomach and nausea: watering mouth and frequent swallowing to avoid vomiting	Abdominal pain or cramps; occasional diarrhea and uncomfortable urge to defecate
2	Episodes of vomiting, possibly including dry heaves; severe nausea and possibility of continued vomiting	Frequent diarrhea and cramps; continuing defecation
3	Protracted or continued vomiting, including dry heaves	Uncontrollable diarrhea and urination; painful cramps
4		

Severity	Cardiovascular	Immune
0	No observable injury	No observable injury
1	Slight feeling of light headedness	Slight fever and headache
2	Unsteadiness upon standing quickly; possible microhemorrhaging	Aching joints; fever; lack of appetite; sores in mouth/throat

3	Severe dizziness; faints upon standing quickly; may have difficulty stopping any bleeding	High fever results in shakes, chills and aches all over
4	Shock; rapid and shallow breathing; skin cold, clammy and very pale; difficulty or inability to stop any bleeding; crushing chest pain	Delirium from fever; overwhelming infections

Table 120. Cutaneous Radiation Symptoms Severity Levels

Severity	Cutaneous
0	No observable injury
1	Itching, sensation of heat, erythema, slight edema
2	Subcutaneous edema, blister formation, epilation
3	Ischemia, ulceration, substantial pain, possible skin necrosis
4	(none)

AMedP-8(*C*) Symptom Progressions and Injury Profiles

Each of the dose ranges from Table 117 and Table 118 is modeled as corresponding to a progression of injury over time. For *AMedP-8*(*C*), the first step to producing Injury Profiles was to generate symptom progressions, which function identically to an Injury Profile except that they only apply to a single physiological system. In all the symptom progression and Injury Profiles shown below, the "no observable injury" progressions are not shown; all Injury Severity Levels on those would be 0 for the duration of time observed.

Table 121 to Table 124 present symptom progressions by dose range for whole-body radiation exposure. The symptom progressions are derived from those originally incorporated in the IDP.[475] Injury Profiles (Table 125) were developed by overlaying the symptom progressions for a given dose range and mapping the highest severity from any physiological system into the Injury Profile. Injury Profiles[476] for cutaneous radiation exposure are in Table 126. The cutaneous profiles are derived from those originally derived from CDC, "Cutaneous Radiation Injury." Both sets of profiles were further modified based on subject-matter input and expertise[477] during the development of *AMedP-8*(*C*).

Table 121. *AMedP-8*(*C*) Symptom Severity by Physiological System for Whole-Body Radiation Dose Range 1.25 – <3 Gy

475 The referenced symptom progressions are included in Levin, *Effects of Combined Injuries*, A-2–A-13.

476 Symptom progressions for cutaneous radiation exposure are not presented separately because there is only one physiological system involved (skin), and therefore the Injury Profile and symptom progression would be identical.

477 Burr et al., *Nuclear Human Response SME Review Meeting*, 1–31; and Burr et al., *Radiological Human Response SME Review Meeting*, 1–16.

Time Point (hr)	Physiological System			
	Upper GI	Lower GI	Cardiovascular	Immune
1	0	0	0	0
3	1	0	0	0
20	0	0	0	0

Table 122. *AMedP-8*(*C*) Symptom Severity by Physiological System for Whole-Body Radiation Dose Range 3 – <5.3 Gy

Time Point (hr)	Physiological System			
	Upper GI	Lower GI	Cardiovascular	Immune
1	0	0	0	0
2	2	0	0	0
5	3	0	0	0
8	2	0	0	0
20	1	0	0	0
30	0	0	0	0
200	0	2	1	0
500	0	2	2	2
700	0	2	2	3

Note: This table reflects the *AMedP-8*(*C*) dose ranges by showing 3 – < 5.3 Gy; in *AMedP-7.5* the range has been changed to 3 – < 4.5 Gy to better align with the $LD_{50/60}$, as discussed in Subsection 0.

Table 123. *AMedP-8*(*C*) Symptom Severity by Physiological System for Whole-Body Radiation Dose Range 5.3 – <8.3 Gy

Time Point (hr)	Physiological System			
	Upper GI	Lower GI	Cardiovascular	Immune
0.3	1	0	0	0
0.7	2	0	0	0
2	3	0	0	0
20	2	0	0	0
50	1	0	0	0
70	0	0	0	0
90	0	0	1	0
100	0	0	2	2
200	0	3	3	2
400	1	3	3	3
600	1	3	4	4

Note: This table reflects the *AMedP-8*(*C*) dose ranges by showing 5.3 – <8.3 Gy; in *AMedP-7.5* the range has been changed to 4.5 – <8.3 Gy to better align with the $LD_{50/60}$, as discussed in Subsection 0.

Table 124. *AMedP-8*(*C*) Symptom Severity by Physiological System for Whole-Body Radiation Dose Range ≥ 8.3 Gy

Time Point (hr)	Physiological System			
	Upper GI	Lower GI	Cardiovascular	Immune
0.3	3	0	0	0
4	3	0	3	0
20	2	0	3	0
50	1	0	3	2
60	1	3	3	2
70	0	3	3	2
100	2	3	3	2
200	2	3	4	3
600	2	3	4	4

Table 125. *AMedP-8*(*C*) Whole-Body Radiation Injury Profiles

Time Point (hr)	Dose Range			
	1.25 – <3 Gy	3 – <5.3 Gy	5.3 – <8.3 Gy	≥8.3 Gy
0.3	0	0	1	3
0.7	0	0	2	3
2	0	2	3	3
3	1	2	3	3
5	1	3	3	3
8	1	2	3	3
20	0	1	2	3
30	0	0	2	3
50	0	0	1	3
70	0	0	0	3
90	0	0	1	3
100	0	0	2	3
200	0	2	3	4
600	0	2	4	4
700	0	3	4	4

Note 1: This table reflects the *AMedP-8*(*C*) dose ranges by showing 5.3 – <8.3 Gy; in *AMedP-7.5* the range has been changed to 4.5 – <8.3 Gy to better align with the $LD_{50/60}$, as discussed in Subsection 0.

Note 2: This table also reflects some corrections to editorial mistakes in *AMedP-8*(*C*) that resulted in the 5.3 – <8.3 Gy Injury Profile being inconsistent with the underlying symptom progressions.

Table 126. *AMedP-8*(*C*) Cutaneous Radiation Injury Profiles

Time Point (hr)	Dose Range			
	2 – <15 Gy	15 – <40 Gy	40 – <550 Gy	≥550 Gy
0.1	0	0	0	1
1	0	0	1	1
8	0	1	1	1
10	1	1	1	1
20	1	1	1	2
50	0	0	2	2
200	0	0	3	3

AMedP-7.5 Injury Profiles

During the development of *AMedP-8*(*C*), the time points in the radiation-related symptom progressions and Injury Profiles were often rounded from an even number of days to one significant digit, for example, from 48 hours (2 days) to 50 hours, or from 96 hours (4 days) to 100 hours. Since the time resolution of output reporting in *AMedP-7.5* is 1 day, such rounding is unwise. Thus, some time points in the Injury Profiles in *AMedP-7.5* differ from those in *AMedP-8*(*C*) to undo the rounding that was performed in the development of *AMedP-8*(*C*). Table 127 and Table 128 show the *AMedP-7.5* Injury Profiles, with the time points that were "un-rounded" in red.

Table 127. *AMedP-7.5* Whole-Body Radiation Injury Profiles

Time Point (hr)	Dose Range			
	1.25 – <3 Gy	3 – <4.5 Gy	4.5 – <8.3 Gy	≥8.3 Gy
0.3	0	0	1	3
0.7	0	0	2	3
2	0	2	3	3
3	1	2	3	3
5	1	3	3	3
8	1	2	3	3
24	0	1	2	3
30	0	0	2	3
48	0	0	1	3
72	0	0	0	3
90	0	0	1	3
96	0	0	2	3
192	0	2	3	4
600	0	2	4	4
696	0	3	4	4

Table 128. *AMedP-7.5* Cutaneous Radiation Injury Profiles

Time Point (hr)	Dose Range			
	2 – <15 Gy	15 – <40 Gy	40 – <550 Gy	≥550 Gy
0.1	0	0	0	1
1	0	0	1	1
8	0	1	1	1
10	1	1	1	1
24	1	1	1	2
48	0	0	2	2
192	0	0	3	3

Medical Treatment (*AMedP-7.5 Table 4-51, Table 4-54*)

Efficacy of Medical Treatment

The efficacy of medical treatment in terms of its effect on the whole body LD_{50} is discussed in Subsection 0. Although certain elements of medical treatment for both whole body and cutaneous radiation injury may temporarily alleviate symptoms, that someone is receiving medical treatment means he or she will not RTD until completely recovered from the injury. Thus, short-term reductions in symptom severity, for example as a result of anti-emetics or painkillers, are not relevant for *AMedP-7.5*.

Although recovery from the whole-body HP subsyndrome begins within a month or two post-irradiation, it is currently unknown how long *complete* recovery from sublethal ARS takes—a long convalescence is generally assumed. Further, ARS is typically defined based on a 60-day window post-irradiation, but the "longer term" (or non-ARS) effects are not necessarily years later—they can begin shortly after the end of the 60-day window. Given the lack of data on and expected high variability in ARS recovery time, we did not include RTD in the whole-body or cutaneous radiation models other than those indicated by the Injury Severity Level returning to (and remaining at) zero. Therefore, there was no reason to attempt to model the efficacy of medical treatment in terms of potentially reducing the time until RTD.

For cutaneous radiation injury, all available treatment is supportive in nature and will not accelerate recovery beyond the timelines shown in the Injury Profiles.

MTOR Tables

Table 129 and Table 130 are the MTOR tables for whole-body and cutaneous radiation casualties, respectively.

The time until CONV for whole-body radiation dose range 1.25 – <3 Gy is based on the time until the symptoms return to Injury Severity Level 0 in the Injury Profile, consistency with *AMedP-7.5*'s reporting rules from Table 15, and the assumption that such a casualty would be CONV rather than RTD because of the potential for later-onset symptoms (since the dose would likely not be known with much certainty). Although such

casualties would certainly be able to RTD at some point, there was no firm basis for setting a time for their RTD in the model, so they are left as CONV. The time until CONV for higher dose ranges is based on the approximate time at which repopulation of the HP stem cells begins—the time at which critical danger due to immunosuppression has passed and it is anticipated that casualties could leave the hospital and undergo outpatient care.

The time until RTD for cutaneous radiation dose ranges 2 – <15 Gy and 15 – <40 Gy are based on the time at which the Injury Severity Level returns to 0 in the Injury Profile and consistency with *AMedP-7.5*'s reporting rules from Table 15. Since cutaneous radiation injury is not life threatening and the supportive care that would be provided can either be completed within a few days or continued as part of outpatient care, casualties in the highest two dose ranges are estimated to become CONV on Day 3.

Table 129. Whole-Body Radiation Medical Treatment Outcome Reporting

Dose Range (Gy)	DOW[a]	CONV[a]	RTD[a]
1.25 – <3	0%	Day 2: 100%	0%
For Treatment Excluding Granulocyte-Colony Stimulating Factor (G-CSF)			
3 – 6.8	0%	Day 30: 100%	0%
≥6.8	Rad: See *AMedP-7.5* Equation 4-32[b] Nuclear: 100%[b]	Rad: Day 30: 100% of WIAs that do not DOW	0%
For Treatment Including G-CSF			
3 – 8.5	0%	Day 30: 100%	0%
≥8.5	Rad: See *AMedP-7.5* Equation 4-32[b] Nuclear: 100%[b]	Rad: Day 30: 100% of WIAs that do not DOW	0%

[a] Reported values indicate the fraction that changes status on a given day; they are not cumulative.

[b] *AMedP-7.5* Equations 4-33 and 4-35 estimate time of death for radiological and nuclear DOWs, respectively.

Table 130. Cutaneous Radiation Medical Treatment Outcome Reporting

Dose Range (Gy)	DOW[a]	CONV[a]	RTD[a]
2 – <15	0%	0%	Day 3: 100%
15 – <40	0%	0%	Day 3: 100%
40 – <550	0%	Day 3: 100%	0%
≥550	0%	Day 3: 100%	0%

[a] Reported values indicate the fraction that changes status on a given day; they are not cumulative.

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1.16. Nuclear Blast Model (*AMedP-7.5 Section 4.4.3*)

Introduction

Nuclear events cause a combination of injuries due to the prompt nuclear effects—radiation, blast overpressure, and thermal energy—resulting from the detonation. Further, there are secondary effects (tumbling, missiling, and building collapse due to secondary, tertiary, and quaternary dynamic pressures) and indirect effects (flash blindness and burns due to secondary fires) that result from the detonation. Even with the experience of Hiroshima and Nagasaki, there is little information to facilitate the estimation of casualties. In part, this is due both to technological advances in the weapons and to differences in the environments in which they might be utilized. *AMedP-7.5* therefore estimates casualties based solely on prompt effects and does not consider secondary or indirect effects (with the exception of death due to tumbling—a tertiary effect). This chapter discusses the blast-overpressure injury model; the next chapter discusses the thermal fluence injury model.

Limitation and Constraints (*AMedP-7.5 Section 4.4.3.2*)

Limitation: Secondary effects (missiling) are not included in any way.

Missiling could theoretically be modeled if the modeling software tracks every object that could become a missile as a result of blast overpressure. Most software does not do so. Further, there is very little data to support modeling of casualties resulting from missiling.

Constraint: The blast model primarily accounts for primary blast effects (static overpressure, or barotrauma).

Constraint: It also uses the blast static overpressure as an index to partially account for tertiary effects (whole-body translation and decelerative tumbling); additional KIAs are estimated as a function of weapon yield.

These two constraints specify the subset of blast effects that are included. These effects are included because there is sufficient data to do so. However, the data for tertiary blast effects are sufficiently limited that tertiary effects can be considered in only the rudimentary manner described.

Physiological Effects (*AMedP-7.5 Table 4-55*)

Within the first millisecond after a nuclear detonation, a fireball composed of the gaseous weapon residue and surrounding air is generated under extremely high pressures and temperature. The rapidly expanding fireball compresses the air in front of it, generating a shock, or high-pressure blast, wave that travels radially outward from the center of the explosion. The main characteristic of this wave is a rapid rise in peak static overpressure (i.e., the maximum pressure in excess of the ambient air pressure). The magnitude of the peak overpressure tends to decrease exponentially as it travels away from the detonation point. In addition, a dynamic pressure front, in the form of a blast wind, is generated by the

blast wave and follows immediately behind it. The dynamic pressure is proportional to the density of air behind the shock wave and to the square of the wind velocity. Both the static overpressure and the dynamic pressure rapidly decrease to zero with time.[478]

An ideal blast wave consists of a positive overpressure rapidly rising (near instantaneously) to its peak value, before decaying exponentially, followed by a less intense negative pressure phase (i.e., pressure less than the ambient air pressure). A key difference between conventional and nuclear explosions is the duration of the positive-pressure phase: for conventional explosives this time is measured in tens of milliseconds, but the positive phase for nuclear blasts lasts on the order of hundreds to thousands of milliseconds depending on yield.[479]

Blast waves can reflect off solid surfaces such as walls. The resulting combination of incident and reflected blast waves can be as much as twice the peak overpressure of the incident wave alone. Due to such factors as multiple reflections and time delays, more complex waveforms can be generated inside open structures (e.g., foxholes or open-sided buildings) or in enclosures with small openings. The potential and type of primary blast injuries are highly dependent upon the nature of the resulting complex waves.

The static overpressure is responsible for the primary blast effects and injuries, while dynamic pressure primarily produces secondary and tertiary blast effects and injuries. Each of these blast injuries will be discussed in turn.

Primary Blast Injuries

In general, the probability of a direct, or primary, blast injury increases with the duration of the blast wave's positive-pressure phase for a given peak overpressure. The relationship between the duration of the positive phase and the potential for injury, however, only holds up to a certain time duration, beyond which the peak static overpressure alone plays a significant role. For expected yields and under most conditions, this time is exceeded for nuclear explosions; as a result, the potential for primary blast injuries is driven by the effective (i.e., the sum of incident and any reflected blast waves) peak static overpressure and the rapidity of its rise.

The pathology of the primary blast injuries is understood from animal testing with nuclear and conventional explosives and human data gathered from military and terrorist conventional explosive events. The principal damage caused by the static overpressure is to air- and gas-filled organs of the body: in particular the auditory system, the upper

478 Glasstone and Dolan, *Effects of Nuclear Weapons*, 80–83.

479 James H. Stuhmiller, Yancy Y. Phillips III, and Donald R. Richmond, "The Physics and Mechanisms of Primary Blast Injury," in *Conventional Warfare: Ballistic, Blast, and Burn Injuries*, ed. Ronald F. Bellamy and Russ Zajtchuk, *Textbook of Military Medicine, Part I: Warfare, Weaponry, and the Casualty* (Falls Church, VA: Department of the Army, Office of the Surgeon General, Borden Institute 1998), 249; and Richmond and Damon, *Primary Blast Injuries*, 28.

respiratory tract and lungs, and the upper and lower gastrointestinal tracts. Injuries to other organs typically are related to or caused by initial disruption to these organs. The organs have three characteristics in common: they mark areas of differing tissue density, they are filled with air or gas, and they assist in equilibrating air pressure within the body.

The auditory system is the most easily affected, with rupture of the tympanic membrane possible at fairly low static overpressures (around 34 kPa). However, in *AMedP-7.5*, this injury is considered as a nuisance effect—it may or may not produce any pain and it may not lead to hearing loss. The blast wave may also damage the cochlea, leading to temporary or permanent hearing loss; in the absence of sufficient data, however, this injury too is neglected.[480]

Among the most serious primary effects of blast are injuries to the respiratory system, which tend to be hemorrhagic in nature. Pulmonary hemorrhages can range from a few pin-head sized petechiae to a concentration of petechiae on the surface of the lung, to confluent hemorrhaging entailing small areas of the lungs or encompassing entire lobes. Some evidence suggests that these blast forces may also produce pulmonary edema, although other research disputes this notion.[481] Under sufficiently high pressures, the lungs may rupture or be punctured by the jagged ends of fractured ribs. In the upper respiratory tract, the mucosal lining of the trachea, larynx, pharynx, and sinus may become bruised or, given sufficient static overpressure, even hemorrhage, leading to constriction of the airways.[482]

More serious still, disruption to the alveoli in the lungs can lead to the introduction of air emboli into the circulatory system. Evidence suggests that the likelihood of significant embolism increases with the severity of the pulmonary hemorrhage.[483] Air emboli in the coronary vessels can lead to cardiac damage similar to a heart attack. Should these air bubbles reach the brain, they can lead to damage to the central nervous system and to stroke-like effects. Embolism is believed to be the leading cause of early death in primary blast injury victims.[484]

After the respiratory system, blast waves do the most damage to the gastrointestinal system. At low static overpressure, the damage can be limited to light contusions to the

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480 Douglas D. Sharpnack, Anthony J. Johnson, and Yancy Y Phillips III, "The Pathology of Primary Blast Injury," in *Conventional Warfare: Ballistic, Blast, and Burn Injuries*, ed. Ronald F. Bellamy and Russ Zajtchuk, *Textbook of Military Medicine, Part I: Warfare, Weaponry, and the Casualty* 271–294 (Falls Church, VA: Department of the Army, Office of the Surgeon General, Borden Institute 1998), 290–292; and Richmond and Damon, *Primary Blast Injuries*, 24.

481 Sharpnack, Johnson, and Phillips, "The Pathology of Primary Blast Injury," 279–280.

482 For more on the primary blast effects on the respiratory system, see Sharpnack, Johnson, and Phillips, "The Pathology of Primary Blast Injury," 273–83; Richmond and Damon, *Primary Blast Injuries*, 14; and Levin, *Effect of Combined Injuries*, 28–29.

483 Sharpnack, Johnson, and Phillips, "The Pathology of Primary Blast Injury," 284–285.

484 Ibid., 284–286; and Richmond and Damon, *Primary Blast Injuries*, 25.

serosal tissue. As the static overpressure increases, injury can range from submucosal contusions, with or without rupture of the mucosal membrane, up to hemorrhages ranging from small petechiae to large hematomas within the intestinal or gastric walls. Finally, at high enough static overpressures, perforations of the intestinal wall can develop, emptying the contents of the gastrointestinal tract into the abdominal cavity and leading to peritonitis after several days.[485]

Other primary effects of blast may include contusions or hemorrhaging of solid organs, such as the heart, liver, spleen, and kidney. At very high pressures, these organs may rupture. In the case of the heart, these effects are most likely due to contact with the lungs as the latter are violently contorted by the blast wave. Similarly, the liver, spleen, and kidney are most likely damaged by coming into contact with the over-expanded gastrointestinal tract.[486] Due to the absence of sufficient data, however, these effects are neglected in *AMedP-7.5*. Orbital "blow-out" fractures have been reported in certain animal species at very high pressures (greater than 690 kPa), but their presence has not been reported in humans.[487] Given the lack of data and the high pressures at which these injuries reportedly occur, this effect is ignored as well. Current research also suggests that pressures arising from conventional explosions may produce traumatic brain injury; but again, the lack of data currently prohibits the inclusion of this effect in *AMedP-7.5*. But any of the effects now excluded from *AMedP-7.5* could easily be included given sufficient data.

Finally, the body is able to adjust (within limits) to relatively gradual changes in external air pressure. Thus, when individuals are in certain locations—such as open structures and enclosures—where the rise time of the static overpressure may be more gradual than that obtained in the open or in the presence of single reflective surfaces, organs may be able to sustain much higher total pressures than would be typical without sustaining significant damage.[488] Due to the uncertainties involved in the specifics of any given scenario, these situations are not included in *AMedP-7.5*; however, if suitable data become available, this protective effect could be included using protection factors (additional lines could be added to *AMedP-7.5* Table 2-8.)

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485 Sharpnack, Johnson, and Phillips, "The Pathology of Primary Blast Injury," 288–289; Richmond and Damon, *Primary Blast Injuries*, 21; and Levin, *Effect of Combined Injuries*, 29.

486 Richmond and Damon, *Primary Blast Injuries*, 21

487 Ibid., 24–25; and Sharpnack, Johnson, and Phillips, "The Pathology of Primary Blast Injury," 289.

488 Richmond and Damon, *Primary Blast Injuries*, 35; Clayton S. White, I. G. Bowen, and Donald R. Richmond, *A Comparative Analysis of Some of the Immediate Environmental Effects at Hiroshima and Nagasaki,* CEX-63.7 (Washington, DC: U.S. Atomic Energy Commission, August 1964), 10–11.

Secondary Blast Injuries

Secondary blast injuries result from the impact of debris energized by blast pressures, winds, ground shock, and gravity. Debris may include building and other structural fragments, as well as missiles generated from building material (e.g., glass fragments) or from the natural terrain (wood, stones, etc.). Secondary effects include both blunt and penetrating trauma. Resulting injuries can range from slight lacerations to perforating lesions to crushing injuries. The type and probability of secondary blast injuries are dependent upon a variety of factors, including the size, shape, mass, density, and nature of the debris; the velocity of the debris; the angle at which impact occurs; the portion of the body involved in the impact; and whether the blow is piercing, penetrating, or nonpenetrating (i.e., crushing).[489] To model secondary effects, much more detail regarding posture, orientation, environment, and many other factors would need to be provided for each scenario than is currently required for *AMedP-7.5*. Given the uncertainties involved in such factors as predicting the type and characteristics of debris, and in the absence of any generalized dynamic pressure threshold values for injury or death, secondary blast injuries are neglected in *AMedP-7.5*.

Tertiary Blast Injuries

Tertiary blast injuries result from whole-body translation (i.e., individuals being propelled through the air by the blast winds). Most of the damage resulting from tertiary blast effects occurs during the deceleration phase and is highly dependent on whether the individual's movement is stopped abruptly by striking a solid object (e.g., a wall or the ground) or more gradually by tumbling along the open ground. Injuries can include contusions, abrasions, lacerations, fractures, damage to internal organs, and even death.[490] The type and probability of tertiary blast injuries are dependent upon a number of factors, including the yield of the nuclear weapon (which helps determine the duration of the blast wind), the posture of the individual (e.g., standing or prone), the orientation of the body to the blast (from perpendicular to parallel), the body's final airborne velocity, the length of time the body is airborne, the hardness of the solid object struck (for abrupt deceleration), the angle of impact, and the organs impacted.[491] Again, to fully model tertiary effects, much more detail would need to be provided for each scenario than is currently required for *AMedP-7.5*. Given the uncertainties involved in such factors as predicting the proximity of solid objects to impact against or the orientation of individuals to the blast wave, and in the absence of any generalized dynamic pressure threshold values for injury, tertiary blast

489 Marvin K. Drake et al., *An Interim Report on Collateral Damage*, DNA 4734Z (La Jolla, CA: Science Applications, Inc., for the Defense Nuclear Agency, October 1978), 5-72.

490 Alt, Forcino, and Walker, "Nuclear Events and Their Consequences," 6.

491 Drake et al., *Collateral Damage*, 2-10; and Glasstone and Dolan, *Effects of Nuclear Weapons,* 553.

injuries are largely neglected in *AMedP-7.5*. However, a tertiary blast threshold for death due to tumbling is considered—see Section 0 for modeling details.

Insult Ranges (*AMedP-7.5 Table 4-55*)

The dose and insult ranges are based on and condensed from the original Injury Severity Category tables included in *AMedP-8*(*A*). In those tables, the various insult-driven injury severities were represented by eight static blast overpressure insult ranges. Discussions with the NATO CBRN Medical Working Group, however, suggested that this was too many ranges. Moreover, these discussions suggested that dose ranges should ideally be clinically differentiable, which did not appear to clearly be the case with the ranges found in *AMedP-8*(*A*).

The development of the new blast insult ranges began by focusing only on effects due to static overpressure. The eight blast insult ranges from *AMedP-8*(*A*) were then condensed into five ranges based on threshold injury-causing pressure values in the auditory, upper gastrointestinal, and respiratory systems found in a variety of sources: the original IDP methodology; a 1978 study prepared for the Defense Nuclear Agency by Drake et al.; and input from NATO subject-matter experts. In this manner, values were found for various levels of auditory, gastrointestinal, and respiratory damage (including, in some cases, burdening dose (BD) values) as well as for 50% (or median) incidence of lethal dose (LD_{50}) at various postures and orientations of the body relative to the blast wave.[492] Table 131 provides a description of effects at various overpressure values, accompanied by citations for each value and effect.

The final insult ranges for *AMedP-7.5* are shown in Table 132; note that the symptom descriptions are derived from Section 0 of this chapter.

[492] NATO, *AMedP-8*(*C*), 3-8; Levin, *Effect of Combined Injuries*, 30–32; and Drake et al., *Collateral Damage*, 5-65–5-71.

Table 131. Symptoms by Blast Overpressure Values

Blast Insult (kPa)	Description
0	Begin Range 1
~ 48	No observable GI tract injury (Drake, 1979; Richmond, 1991; Levin, 1993)
50	End Range 1 – Begin Range 2
~50	BD_{01} Tympanic membrane casualty (Drake, 1979)
~70	No observable lung injury (Drake, 1979; Richmond, 1991; Levin, 1993)
100–140	BD_{50} Tympanic membrane casualty (Drake, 1979)
140	End Range 2 – Begin Range 3
~160	Moderate GI injury—small area submucosal contusions (Richmond, 1991; Levin 1993)
~200	Moderate lung injury—<30% area confluent (Richmond, 1991; Levin, 1993)
240	End Range 3 – Begin Range 4
~260	Very severe GI injury—disruption of mucosal layer with perforation, hemorrhage or rupture (Richmond, 1991; Levin, 1993)
~260	LD_{50}—perpendicular to blast wave (Bowen)
290	End Range 4 – Begin Range 5
~290	LD_{50} (PRCC, 2013)
~290	Very severe lung injury—>60% lung area and/or entire lobes confluent (Richmond, 1991; Levin, 1993)
~440	LD_{50}—prone and parallel to blast wave (Bowen)

Sources: Levin, *The Effect of Combined Injuries*; Richmond and Damon, *Primary Blast Injuries*; Drake et al., *An Interim Report on Collateral Damage*; U.S. Department of the Army, *Personnel Risk and Casualty Criteria*; and I. G. Bowen, E. R. Fletcher, and D. R. Richmond, Estimate of Man's Tolerance to the Direct Effects of Air Blast, DASA 2113 (Washington, DC: Defense Atomic Support Agency, October 1968).

Table 132. Blast Insult Ranges

Blast Insult Range (kPa)	Set of Symptoms
<50	No observable injury
50 – <140	Eardrum rupture in 50%; threshold lung damage; threshold gastrointestinal damage
140 – <240	Burdening level lung damage in 50%; burdening level tympanic membrane rupture in 90%
240 – <290	Burdening level lung damage in 90%; lethality in 10%
≥290	Lethality in ≥50%

Injury Profiles (*AMedP-7.5 Table 4-56*)

The following sections explain the historical development of the symptom progressions and Injury Profiles for *AMedP-8*(*C*) and the slight changes to the Injury Profiles for *AMedP-7.5*.

Severity Levels and Symptoms

The first part of the process for *AMedP-8*(*C*) was deciding which physiological systems would be represented in the model. The IDP methodology recommended including upper gastrointestinal, lower gastrointestinal, fatigability and weakness, hypotension, and upper respiratory infection. These symptoms were represented on a severity scale of 1–5.[493] Because the IDP severity scales were independent for each physiological system, the next step was to "translate" them to the injury severity scale and physiological systems to be used for *AMedP-8*(*C*) (see Table 2). The result of this effort is shown in Table 133.

Table 133. Blast Overpressure Symptoms and Severity Levels

Severity	Upper Gastrointestinal	Lower Gastrointestinal	Respiratory
0	No observable injury	No observable injury	No observable injury
1	Upset stomach and nausea: watering mouth and frequent swallowing to avoid vomiting	Abdominal pain or cramps; occasional diarrhea and uncomfortable urge to defecate	Mild shortness of breath
2	Episodes of vomiting, possibly including dry heaves; severe nausea and possibility of continued vomiting	Frequent diarrhea and cramps; continuing defecation	Frank shortness of breath, respiratory congestion, nonproductive cough
3	Protracted or continued vomiting, including dry heaves	Uncontrollable diarrhea and urination; painful cramps	Air hunger; labored breathing; breathing sporadically stops and starts; hemoptysis
4			Breathing stops completely or struggling to breathe; cyanosis; prostration

AMedP-8(*C*) Symptom Progressions and Injury Profiles

Each of the dose ranges from Table 132 is modeled as corresponding to a progression of injury over time. For *AMedP-8*(*C*), the first step to producing Injury Profiles was to generate symptom progressions, which function identically to an Injury Profile except that they only apply to a single physiological system. But upon generating symptom progressions for each insult range, it became apparent that based on the limited data available, the respiratory symptoms were the most severe in every insult range and at all time points and thus would determine the injury severity for the Injury Profile. Thus, symptom progressions for the upper and lower gastrointestinal tract and cardiovascular system were not included in *AMedP-8*(*C*).

493 Levin, *Effect of Combined Injuries*.

The Injury Profiles shown below were derived from several sources: those originally incorporated in the IDP,[494] a 1978 study prepared for the Defense Nuclear Agency by Drake et al.,[495] and input from NATO subject-matter experts.[496] They can be viewed as equivalent to a symptom progression for respiratory symptoms. The "no observable injury" Injury Profile is not shown in Table 134 since the Injury Severity Level would be 0 for the entire duration of time.

Table 134. *AMedP-8*(*C*) Primary Nuclear Blast Injury Profiles

Time Point (hr)	Insult Range			
	50 – <140 kPa	140 – <240 kPa	240 – <290 kPa	≥290 kPa
0.1	2	3	3	4
30	2	2	3	4
40	1	2	3	4
200	0	1	3	4
300	0	1	2	4
400	0	0	1	4
700	0	0	0	4

AMedP-7.5 Injury Profiles

During the development of *AMedP-8*(*C*), the time points in the blast-related symptom progressions and Injury Profiles were often rounded from an even number of days to one significant digit, for example from 48 hours (2 days) to 50 hours, or from 96 hours (4 days) to 100 hours. Since the time resolution of output reporting in *AMedP-7.5* is 1 day, such rounding is unwise. Thus, some time points in the Injury Profiles in *AMedP-7.5* differ from those in *AMedP-8*(*C*) to undo the rounding that was performed in the development of *AMedP-8*(*C*). Table 135 shows the *AMedP-7.5* Injury Profiles, with the time points that were "un-rounded" in red. Finally, the 0.1 hr time point was changed to 0.25 hr simply to reduce the size of the table, since the 0.25 hr time point had to be added to represent the modeled time to death for the ≥290 kPa Injury Profile, and the 0.1 hr time point would only present information also given in the 0.25 hr time point.

494 Levin, *Effect of Combined Injuries*.

495 Drake et al., *Collateral Damage*.

496 Burr et al., *Nuclear Human Response SME Review Meeting*.

Table 135. *AMedP-7.5* Primary Nuclear Blast Injury Profiles

Time Point (hr)	Insult Range			
	50 – <140 kPa	140 – <240 kPa	240 – <290 kPa	≥290 kPa
0.25	2	3	3	4[a]
30	2	2	3	
40	1	2	3	
192	0	1	3	
288	0	1	2	
408	0	0	1	
696	0	0	0	

[a] Death is modeled to occur at this point, based on the default value of the parameter $T_{death\text{-}CN\text{-}SL4}$ in *AMedP-7.5*.

Lethal Tertiary Effects (*AMedP-7.5 Section 4.4.3.4*)

The following data were derived from work described in Drake et al.[497] To begin, research suggested that the incidence of casualties and death could be described as a function of the velocity achieved by an individual picked up and thrown through the air by the tertiary blast effect known as "whole body translation". Specifically, research indicated that 50% of individuals would become casualties (i.e., median burdening dose (BD_{50})) if thrown at an impact velocity of 4.7 meters/second, and 50% of individuals would die if thrown at an impact velocity of 10.7 meters/second. Impact velocity is dependent upon the amount of force (the strength of the winds, which is a function of overpressure) pushing on the individual and the length of time that this force acts on the individual; both values in turn are highly dependent on the yield of the nuclear weapon.

In addition, the impact velocity is dependent on the posture of the individual at the time the dynamic pressure first strikes and on the orientation of the body relative to the blast. Finally, the damage done to the body depends on the manner in which its movement is stopped: stopping by striking a hard, "non-yielding" vertical surface will, all other things equal, cause more damage than decelerative tumbling. These factors were combined and examined by considering four combinations of target posture and environment: (1) a prone target, at a random orientation to the blast, impacting on a non-yielding surface, after traveling 3 meters; (2) a prone target, at a random orientation to the blast, undergoing decelerative tumbling across an open field; (3) a target standing, either oriented front- or back-on to the wind, impacting on a non-yielding surface, after traveling 3 meters; and (4) a target standing, either oriented front- or back-on to the wind, undergoing decelerative tumbling across an open field.

497 Drake et al., *Collateral Damage*, 5-90–5-106

Based on the minimum static overpressure versus yield required to cause a median casualty (BD_{50}) and a median lethality (LD_{50}) for each of these combinations of posture and environment provided in Drake et al.,[498] the graphs shown in Figures 108 and 109 were generated for yields of interest. In addition, Figure 108 displays the minimum overpressure required to achieve a casualty at Severity Level 2 (WIA(2)) and Severity Level 3 (WIA(3)) as indicated by the blast Injury Profiles.[499] Likewise, the static overpressure value at which individuals reach Severity Level 4 (i.e., are declared dead—in this case KIA) is displayed in Figure 109. These graphs subsequently were provided to the NATO SMEs at the nuclear review meeting held for the purpose of developing the *AMedP-8*(*C*) methodology.

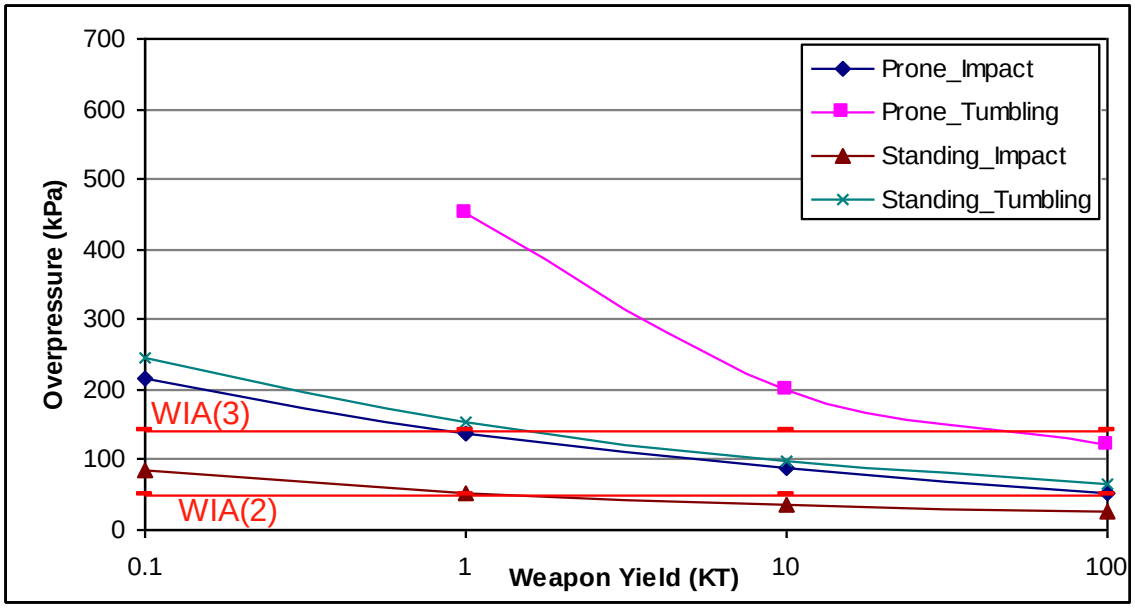


Figure 7. Overpressures Required to Achieve Median Injury (BD_{50}) Due to Translation Effects

498 Ibid., 5-94

499 Note that blast Injury Profiles never begin with Injury Severity Level 1.

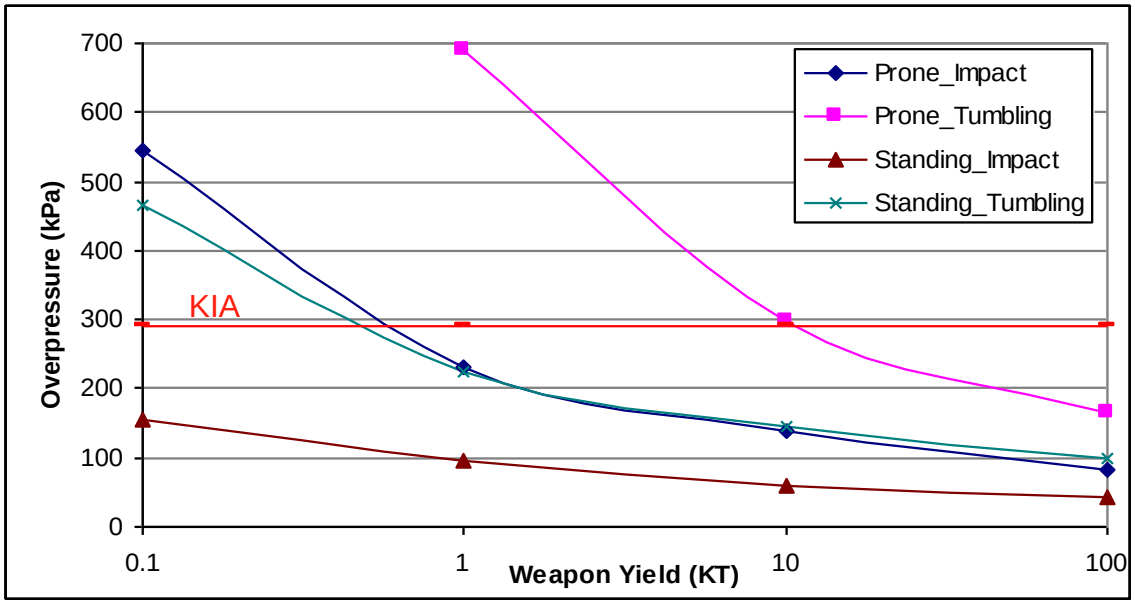
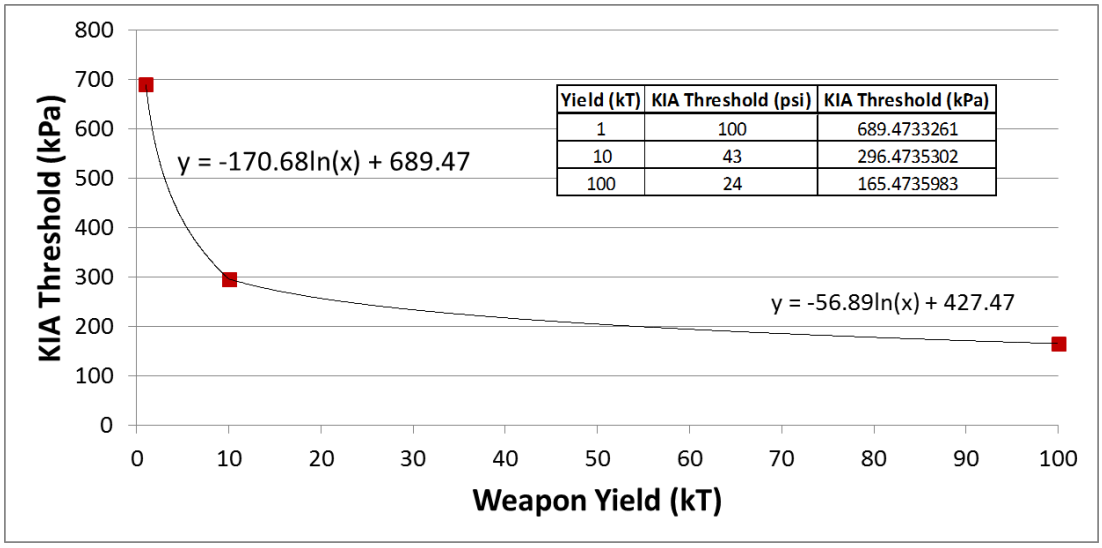


Figure 8. Overpressures Required to Achieve Median Lethality (LD_{50}) Due to Translation Effects

Upon reviewing these graphs, the SMEs agreed to ignore casualties produced by whole-body translation as they generally occurred at static overpressures near or greater than that for the casualties produced by static overpressure alone at Severity Level 2 (the recommended severity level for casualties is Severity Level 1); this was particularly true for targets prone when the winds struck. Most targets, in practice, would be expected to be in a prone posture by the time the dynamic winds struck, as individuals initially standing at the time of a nuclear detonation would likely be knocked to the ground by a low-intensity blast wave that oftentimes precedes the major pressure waves. Similar reasoning led the SMEs to consider only the prone posture for lethality effects. To simplify the problem further, the SMEs agreed to consider only decelerative tumbling for the general casualty-estimation process, although data are available to enable modelers to include prone "impact" cases as well.[500]

Therefore, in *AMedP-8*(*C*) and in *AMedP-7.5*, individuals at icons in the open are classified as KIAs if they are exposed to blast static overpressure exceeding the value required to achieve median lethality due to translation effects for the given weapon yield. Individuals inside some protective structure or vehicle (i.e., icons in vehicles, building structures, tents, or foxholes) are assumed to be shielded from tertiary effects. The specific threshold value as a function of weapon yield is calculated according to *AMedP-7.5* Equation 4-36, the derivation of which is depicted in Figure 9.

500 Burr et al., *Nuclear Human Response SME Review Meeting*, 1–31.



Source: Drake et al., *An Interim Report on Collateral Damage*, 5-94.

Figure 9. Data and Curve Fits Used to Derive *AMedP-7.5* Equation 4-36

Medical Treatment—MTOR (*AMedP-7.5 Table 4-57*)

The time until RTD for the lowest three insult ranges is dictated as the time until the symptoms return to Injury Severity Level 0 in the Injury Profile and consistency with *AMedP-7.5*'s reporting rules (Table 15). For the highest insult range, if *AMedP-7.5*'s default parameters are used, all personnel will be KIA. However, if the user edits the parameters as indicated in Table 136, then a fraction of personnel are estimated to survive.

Although one can find many reports summarizing statistics related to the medical response to terrorist bombings spanning the last several decades, we preferred to use data from military operations because military personnel wear body armor, reducing the incidence and severity of shrapnel wounds unlike for civilian cases (but note that even when using military data, multiple injuries will still occur and confound the data to some unknown extent).

In the best retrospective review of military primary blast injuries we found,[501] the cases reviewed were patients treated in Afghanistan, Iraq, Germany, or continental U.S. military medical facilities after being wounded in an explosion. Although the review included nearly 10,000 patients, blast lung injury and blast intestinal injury only occurred in 172[502] and 5 personnel, respectively. Since the overpressure (or insult range in kPa) for the patients is unknown, and blast lung and blast intestinal injury were the most severe injuries identified in the review, we used the presence of blast lung or blast intestinal injury

501 Amber E. Ritenour et al., "Incidence of Primary Blast Injury in US Military Overseas Contingency Operations," *Annals of Surgery* 251, No. 6 (2010): 1140–1144.

502 Twenty of whom also had tympanic membrane rupture.

as a surrogate for determining which personnel from the review should be considered relevant for determining outcomes for the ≥290 kPa insult range.

Ritenour et al. reported that of the 172 personnel with blast lung injury, 35 eventually returned to duty (time until RTD not reported), and 18 eventually died (time until DOW not reported). For the five personnel with blast intestinal injury, zero returned to duty and two died (time until DOW not reported).[503] Combining the data, 19.7% of personnel were able to RTD, and 11.2% of personnel DOW. To use simple round numbers, *AMedP-7.5* Table 4-57 indicates that for icons in the ≥290 kPa insult range, 10% of personnel DOW, 20% RTD, and the remaining 70% become CONV with no estimated time until RTD.

To estimate the days on which personnel DOW, RTD, or become CONV according to the preceding paragraph, we wanted to use the same sort of dataset as used to determine the fraction of personnel who DOW, RTD, or become CONV, but Ritenour et al. did not present the necessary information, nor were we able to find such information from another source. Even among summaries of civilian casualties of terrorist bombings, we found only one source that provided the needed information for *survivors* whose primary injury was blast lung injury (Hirschberg et al.),[504] and even in this case all victims had other injuries that could have affected the timing of their discharge from the hospital. The only information the report provides that allows one to determine whether the patients likely belong in the ≥290 kPa insult range is that 10 of the 11 required intubation. Since this fits well with Injury Severity Level 4 for *AMedP-7.5*, the length of hospital stay for those 10 patients was used to estimate the time until RTD[505] and CONV for survivors.

The numbers of days until discharge from the hospital for the 10 patients was 8, 11, 15, 16, 19, 31, 36, 50, 79, and 88 days; the average was 35.3 days, and the standard deviation was 28.5 days. To capture the *fact* of variability in time to RTD/CONV without relying too heavily on these 10 specific data points, we split the time to RTD/CONV for the model between the average time rounded to one significant digit (35 days) and 1 week shorter and longer (28 and 42 days). For CONV, which includes 70% of personnel, we arbitrarily assigned 30% to Day 35 and 20% to each of days 28 and 42. Likewise for RTD, which includes 20% of personnel, we assigned 10% to Day 35 and 5% to each of days 28 and 42.

We found no data that could inform the time until DOW, but given the nature of blast injuries we thought it likely that DOWs would occur soon after the blast, so we assigned

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503 Ibid, Table 3.

504 Boaz Hirshberg et al., "Recovery from Blast Lung Injury One-Year Follow-up," *Chest* 116, No. 6 (1999): 1683–1688.

505 Since the data are related to discharge from hospital, using them to estimate time to RTD implies the assumption that upon leaving the hospital, certain people can immediately RTD.

the 10% that DOW should be reported as such on Day 2 (indicating death on Day 1 while following *AMedP-7.5*'s reporting rules from Table 15).

Table 136. Primary Nuclear Blast Medical Treatment Outcome Reporting

Insult Range (kPa)	DOW[a]	CONV[a]	RTD[a]
50 – <140	0%	0%	Day 9: 100%
140 – <240	0%	0%	Day 17: 100%
240 – <290	0%	0%	Day 29: 100%
	If $T_{MTF} \leq T_{death\text{-}CN\text{-}SL4}$		
≥290	Day 2: 10%	Day 28: 20%[b] Day 35: 30%[b] Day 42: 20%[b]	Day 28: 5%[b] Day 35: 10%[b] Day 42: 5%[b]

Note: because this table applies to *primary* blast injuries, modeling of lethal tertiary effects is not affected by the availability of medical treatment.

Note: If $T_{MTF} > T_{death\text{-}CN\text{-}SL4}$ (as is the default—see *AMedP-7.5* Table 4-57), icons in the ≥290 kPa insult range are KIA, so this table is not needed to estimate their outcome.

[a] Reported values indicate the fraction that changes status on a given day; they are not cumulative.

[b] In the personnel status table, these individuals are reported as WIA(3) on Day 2 and remain there until becoming CONV.

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1.17. Nuclear Thermal Fluence Model (*AMedP-7.5 Section 4.4.4*)

Introduction

Nuclear events cause a combination of injuries due to the prompt nuclear effects—radiation, blast overpressure, and thermal energy—resulting from the detonation. Further, there are secondary effects (tumbling, missiling, and building collapse due to secondary, tertiary, and quaternary dynamic pressures) and indirect effects (flash blindness and burns due to secondary fires) that result from the detonation. Even with the experience of Hiroshima and Nagasaki, there is little information to facilitate the estimation of casualties. In part, this is due both to technological advances in the weapons and to differences in the environments in which they might be utilized. *AMedP-7.5* therefore estimates casualties based solely on prompt effects and does not consider secondary or indirect effects (with the exception of death due to tumbling—a tertiary effect). The previous chapter discusses the blast overpressure injury model; this chapter discusses the thermal fluence injury model.

Assumptions, Limitations, and Constraint (*AMedP-7.5 Section 4.4.4.2*)

> **Assumption**: Thermal fluence resulting from a nuclear detonation can be quantitatively correlated to a percentage of body surface area burned, with the percentage being dependent upon the type of uniform or clothing worn and the fit of the garment.

This assumption is necessary to enable calculation of Effective CBRN Challenge. The portion of this assumption that one might question is that it leaves out certain factors, such as body orientation (which is excluded because it is too random to be modelable). NATO SMEs agreed with this approach.[506]

> **Assumption**: The Injury Profile and associated casualty category changes are independent of which body part(s) suffer(s) burns.

This assumption is necessary because challenge models lack the fidelity to estimate which portions of a person would be burned, in part because there is a high level of randomness to this type of injury. Although making this estimate might be possible, it is impractical.

> **Limitation**: The effects of thermal flash (such as flash blindness) are ignored.

See Subsection 0 for explanation.

> **Limitation**: The percentage of body surface area burned excludes first-degree (epidermal or surface) burns.

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506 Burr et al., *Nuclear Human Response SME Review Meeting*.

Constraint: The percentage of body surface area burned includes partial-thickness (second-degree) and full-thickness (third-degree) burns.

This last limitation and the constraint clarify which types of burn are included in the model. First-degree burns are not included because they are probably operationally insignificant—that is, they would have little effect on the ability of a warfighter to do his or her job.

Physiological Effects (*AMedP-7.5 Table 4-60*)

In the aftermath of a nuclear detonation, about one-third of the explosive energy will dissipate as thermal energy. Thermal energy is output in two pulses. The first pulse, which is 1 percent of the total thermal energy, is short in duration, is ultraviolet, and does not contribute significantly to producing casualties. The second wave, which comprises 99 percent of the thermal energy, is infrared, is invisible, and causes the majority of casualties—casualties exhibiting flash burns and interruption in vision.[507] Electromagnetic energy of the thermal pulse travels quickly and in a straight line, so the only possible protection is a barrier or clothing.[508]

Burn Injury

Burn injury severity is classified by the depth of the area burned: first-, second-, and third-degree burns. A first-degree burn is characterized by damage to the epidermal layer of the skin, a skin depth of 100 nanometers. There is immediate pain and redness of skin similar to that from sunburn, and the damage is reversible. There is no loss of fluid.[509] Healing occurs within 2–3 days.

Second-degree burns, or partial-thickness burns, can damage the skin down to the dermal layer. Further differentiation of second-degree burns are as follows: superficial (skin depth of 100–500 nanometers); mid-level (skin depths up to 1,000 nanometers); and deep (skin depths up to 2,000 nanometers). Second-degree burns result in prolonged pain, skin redness, swelling, and blisters. An eschar (scab) will form 6 to 24 hours post-exposure, and eventually full skin regeneration will occur. Second-degree burns will generally heal in 1–3 weeks; as the percent body surface area burned (%BSA) increases, the healing time will increase as well.

Third-degree burns, or full-thickness burns, are characterized by irreversible full-thickness skin damage in skin depths of more than 2,000 nanometers. Skin will appear charred and may lose elasticity. Skin will not regenerate normally; therefore, grafting is necessary. There is no pain at the site of the third-degree burn because the nerve endings have been destroyed; however, there may be some pain in adjacent second-degree burn

507 Levin, *Effect of Combined Injuries*, 20–21.

508 Alt, Forcino, and Walker, “Nuclear Events and Their Consequences,” 8.

509 Levin, *Effect of Combined Injuries*, 22.

areas. The incidence of infection is common. Healing of full-thickness burns is extremely slow and always results in a scar unless new skin is grafted.[510]

In the post-burn period, specifically for second and third-degree burns, there is fluid loss (hypovolemia) and electrolyte imbalance, which leads to a decrease in renal blood flow, followed by decreased cardiac output. As the blood pressure decreases, hemodynamic instability (shock) will occur. There is cell destruction in the burn area and a loss of red blood cells of 5 to 40 percent of the total red blood cell mass, depending on the area and depth of the burn. Lymphocytes are reduced, and the immune system is compromised, resulting in an increased probability of infection.[511] The severity of these symptoms varies depending on the type of burn, the burn location, and the %BSA.

Eye Injury

Flash blindness and retinal burns are common thermal effects. Flash blindness is the depletion of photopigment from the retinal receptors. Flash blindness typically happens when the fireball is indirectly observed (e.g., via reflection). The result is temporary blindness, the duration of which is seconds in daylight and minutes in darkness. Retinal burns occur when the fireball is directly observed, causing a permanent blind spot on the retina. Nonetheless, because (at least partial) vision is restored in approximately the same amount of time in both cases, a retinal burn causes no more time loss to a mission than flash blindness.[512] Since these injuries are posture dependent (i.e., depend on the time of attack, direction the individual is facing, etc.), there are numerous uncertainties that make modeling these effects challenging. Further, since these injuries are seldom life threatening and are typically short lived, retinal burns and flash blindness are neglected in *AMedP-7.5*.

Insult Ranges (*AMedP-7.5 Table 4-60*)

The dose and insult ranges are based on and condensed from the original Injury Severity Category tables included in *AMedP-8*(*A*). In those tables, the various insult-driven injury severities were represented by 11 thermal insult ranges. Discussions with the NATO CBRN Medical Working Group, however, suggested that this was too many ranges. Moreover, these discussions suggested that dose ranges should ideally be clinically differentiable, which did not appear to clearly be the case with the ranges found in *AMedP-8*(*A*).

The process for developing the thermal insult table required translation of thermal fluence to percentage of body surface area (%BSA) burned, shown in Table 137. *AMedP-*

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510 Ibid.

511 Marvin K. Drake and William A. Woolson, *EM-1—Capabilities of Nuclear Weapons, Chapter 14— Effects on Personnel*, DNA-EM-1-CH-14 (San Diego, CA: Defense Nuclear Agency, March 1993), 14-5b.

512 Alt, Forcino, and Walker, “Nuclear Events and Their Consequences,” 7.

8(*A*) referenced the severity of thermal injury solely as a function of thermal fluence; the descriptions referenced the severity of burn as a function of uniform type. The %BSA, however, is what dictates the severity of injury. Changes in uniform type may be expected to alter the percentage of the BSA burned—for example, bare skin has a significantly lower threshold for second-degree (partial thickness) burns (approximately 109 kJ/m2) than skin encased in a standard battle dress uniform (BDU), which fits loosely over a T-shirt (approximately 640 kJ/m2). Thus, physiological descriptions of anticipated injury progressions and symptoms associated with varying percentages of BSA burned were used to derive the thermal insult table.[513]

The final insult ranges for *AMedP-7.5* are shown in Table 138; note that the symptom descriptions are derived in part from Section 0 of this chapter.

Table 137. Thermal Ranges Used in *AMedP-8*(*A*)

Category Number	Exposure Range kJ/m² (cal/cm²)	Description	Abbreviation
1	0–105 (0.0–2.5)	No injury	No Effects
2	105–168 (2.5–4.0)	First degree burn, bare skin	Threshold 1° Bare Skin Burn
3	168–210 (4.0–5.0)	Second degree burn, bare skin	Threshold 2° Bare Skin Burn
4	210–293 (5.0–7.0)	Third degree burn, bare skin	Threshold 3° Bare Skin Burn
5	293–390 (7.0–9.3)	Skin burn, no uniform burn	Extensive Bare Skin Burn
6	394–523 (9.3–12.5)	50 percent incidence second degree burn over 21 percent of the body in battle dress uniform (BDU) + T-shirt	2°, 21% BSA, BDU + T
7	523–787 (12.5–18.8)	50 percent incidence second degree burn over 21 percent of the body in battle dress overgarment (BDO)	2°, 21% BSA, BDO
8	787–842 (18.8–20.1)	50 percent incidence second degree burn over 21 percent of the body in BDU + T-shirt + spacer	2°, 21% BSA, BDU + T + Air
9	842–1,634 (20.1–39.0)	50 percent incidence second degree burn over 21 percent of the body BDO + spacer	2°, 21% BSA, BDO + Air
10	1,634–2,531 (39.0–60.4)	50 percent incidence second degree burn over 21 percent of the body in BDO + BDU + T-shirt	2°, 21% BSA, BDO + BDU + T

513 Levin, *Effect of Combined Injuries*; AFRRI, *Medical Management of Radiological Casualties*; and Baba et al., *Incidence of Skin Burns*.

Category Number	Exposure Range kJ/m^2 (cal/cm^2)	Description	Abbreviation
11	>2,531 (>60.4)	50 percent incidence second degree burn over 21 percent of the body in BDO + BDU + T-shirt + spacer	2°, 21% BSA, BDO + BDU + T + Air

Source: NATO, *AMedP-8*(*A*) *Nuclear*, 3-8.

Note: This table exactly reproduces what is shown in *AMedP-8*(*A*), including what we believe to be a typo for the exposure range for category number 6: the lower bound as shown is 394 kJ/m^2, leaving a gap between it and the upper bound of category number 5 (390 kJ/m^2). We believe the lower bound for category number 6 should have been 390 kJ/m^2.

Table 138. Thermal Insult Ranges

Thermal Insult Range (%BSA)	Set of Symptoms
<1	No observable injury[a]
1 – <10	1st, 2nd and possible third-degree burns; electrolyte imbalance; pain
10 – <20	Upper GI discomfort; first-, second- and possible third-degree burns; electrolyte imbalance; increased pain
20 – <30	Upper GI discomfort; first-, second- and possible third-degree burns; fluid loss; decreased renal blood flow; compromise of the immune system; pain; lethality in 10%[b]
≥30	Upper GI discomfort; second- and third-degree burns; hypovolemia; decreased renal blood flow; shock resulting from blood pressure decrease; cardiac distress; toxemia; multiple organ failure; lethality in ≥50%[b]

[a] <1% BSA may include a larger area of first-degree burns.

[b] Estimation of burn lethality is approximate.

Injury Profiles (*AMedP-7.5 Table 4-61*)

The following sections explain the development of the symptom progressions and Injury Profiles for *AMedP-8*(*C*) and Injury Profile changes for *AMedP-7.5*.

Severity Levels and Symptoms

The first part of the process for *AMedP-8*(*C*) was deciding which physiological systems would be represented in the model. The IDP methodology recommended including upper gastrointestinal, lower gastrointestinal, fatigability and weakness, infection and bleeding, hypotension, and fluid loss. These symptoms were represented on a severity scale of 1–5.[514] Because the IDP severity scales were independent for each physiological system, the next step was to "translate" them to the injury severity scale to be used for *AMedP-8*(*C*) (see Table 2). The result of this effort is shown in Table 133.

Two new systems encompass hypotension and bleeding (cardiovascular system) and infection (immune system). In addition, a skin system was added; this system encompasses both the fluid loss and pain categories previously considered for thermal insults, but also adds a burn severity description. In part, this system was added to allow for the estimation of casualties at the time they would be anticipated to happen as a function of the burn, versus waiting until internal physiological symptoms might be expected to develop as was the case in the IDP methodology.

Table 139. Thermal Fluence Symptoms and Severity Levels

Severity	Cardiovascular	Immune	Skin
0	No observable injury	No observable injury	No observable injury
1	Slightly feeling of light headedness	Slight fever and headache	Epidermal (first degree) burns over small body surface area characterized by skin redness, swelling, and blistering; persistent pain at burn site
2	Unsteadiness upon standing quickly; possible micro-hemorrhaging	Aching joints; fever; lack of appetite; sores in mouth/throat	Partial-thickness (second degree) burns over large body surface area combined with some full-thickness (third degree) burns; pain at sites of partial-thickness burns; potential for fluid loss through burn sites
3	Severe dizziness; faints upon standing quickly; may have difficulty stopping any bleeding	High fever results in shakes, chills and aches all over	Partial- (second degree) and full-thickness (third degree) burns over up to 30% of the body surface area; limited pain due to nerve damage from third-degree burns; significant fluid loss through burn sites

514 Levin, *Effect of Combined Injuries*.

Severity	Cardiovascular	Immune	Skin
4	Shock; rapid and shallow breathing; skin cold, clammy and very pale; difficulty or inability to stop any bleeding; crushing chest pain	Delirium from fever; overwhelming infections	≥30 %BSA with partial- (second degree) and full-thickness (third degree) burns

AMedP-8(*C*) Symptom Progressions and Injury Profiles

Each of the dose ranges from Table 138 is modeled as corresponding to a progression of injury over time. For *AMedP-8*(*C*), the first step to producing Injury Profiles was to generate symptom progressions, which function identically to an Injury Profile except that they only apply to a single physiological system. In all the symptom progression and Injury Profiles shown below, the "no observable injury" progressions are not shown; all Injury Severity Levels on those would be 0 for the duration of time observed.

Table 140 to Table 143 present the symptom progressions by insult range, derived from those originally incorporated in the IDP[515] with modifications based on subject-matter input and expertise[516] during the development of *AMedP-8*(*C*). Presented next are the Injury Profiles (Table 144), which were derived by overlaying the symptom progressions for a given insult range and mapping the highest severity from any physiological system into the Injury Profile.

Table 140. *AMedP-8*(*C*) Symptom Severity by Physiological System for Thermal Fluence Insult Range 1 – <10 %BSA

Time Point (hr)	Physiological System		
	Cardiovascular	Immune	Skin
0.1	0	0	1
50	0	2	1
70	0	2	0
336	0	0	0

515 The referenced symptom progressions are included in Levin, *Effects of Combined Injuries*, A-2–A-13.

516 Burr et al., *Nuclear Human Response SME Review Meeting*, 1–31; and Burr et al., *Radiological Human Response SME Review Meeting*, 1–16.

Table 141. *AMedP-8*(*C*) Symptom Severity by Physiological System for Thermal Fluence Insult Range 10 – <20 %BSA

Time Point (hr)	Physiological System		
	Cardiovascular	Immune	Skin
0.1	0	0	2
20	0	2	2
50	1	2	2
200	0	2	2
336	0	0	1

Table 142. *AMedP-8*(*C*) Symptom Severity by Physiological System for Thermal Fluence Insult Range 20 – <30 %BSA

Time Point (hr)	Physiological System		
	Cardiovascular	Immune	Skin
0.1	0	0	3
6	1	0	3
20	2	0	3
30	2	2	3
50	3	2	3
100	3	3	3
300	2	3	3
400	2	3	2

Table 143. *AMedP-8*(*C*) Symptom Severity by Physiological System for Thermal Fluence Insult Range ≥ 30 %BSA

Time Point (hr)	Physiological System		
	Cardiovascular	Immune	Skin
0.1	1		3
3	2		3
6	3		3
20	4		3
70	4		4

Note: Immune symptoms were neglected for the ≥ 30 %BSA insult range in *AMedP-8*(*C*).

Table 144. *AMedP-8*(*C*) Thermal Fluence Injury Profiles

Time Point (hr)	Insult Range			
	1 – <10 %BSA	10 – <20 %BSA	20 – <30 %BSA	≥30 %BSA
0.1	1	2	3	3
20	1	2	3	4
50	2	2	3	4
336	0	1	3	4

AMedP-7.5 Injury Profiles

During the development of *AMedP-8*(*C*), the time points in the thermal-related symptom progressions and Injury Profiles were often rounded from an even number of days to one significant digit, for example from 48 hours (2 days) to 50 hours, or from 96 hours (4 days) to 100 hours. Since the time resolution of output reporting in *AMedP-7.5* is 1 day, such rounding is unwise. Thus, some time points in the Injury Profiles in *AMedP-7.5* differ from those in *AMedP-8*(*C*) to undo the rounding that was performed in the development of *AMedP-8*(*C*). Table 145 shows the *AMedP-7.5* Injury Profiles, with the time points that were "un-rounded" in red.

Table 145. *AMedP-7.5* Thermal Fluence Injury Profiles

Time Point (hr)	Insult Range			
	1 – <10 %BSA	10 – <20 %BSA	20 – <30 %BSA	≥30 %BSA
0.1	1	2	3	3
24	1	2	3	4[a]
48	2	2	3	
336	0	1	3	

[a] Death is modeled to occur at this point, based on the default value of the parameter $T_{death\text{-}CN\text{-}SL4}$ in *AMedP-7.5*.

Medical Treatment—MTOR (*AMedP-7.5 Table 4-62*)

For the 1 – <10 %BSA insult range, the Injury Profile returns to zero, so that time and the *AMedP-7.5* reporting rules from Table 15 were used to estimate the time until RTD. For the other insult ranges, we used an equation that predicts hospitalization time generated by experts who reviewed the cases of 352 patients[517] and verified the results with an equation we derived based on summary data presented for 937 patients.[518] Note that hospitalization time could correlate to time until CONV or time until RTD, depending on

517 M. K. Wong and R. C. K. Ngim, "Burns Mortality and Hospitalization Time—A Prospective Statistical Study of 352 Patients in an Asian National Burn Centre," *Burns* 21, no. 1 (1995): 39–46.

518 P. William Curreri, Arnold Luterman, David W. Braun, and Thomas Shires, "Burn Injury. Analysis of Survival and Hospitalization Time for 937 Patients," *Annals of Surgery* 192, no. 4 (1980).

the patient, and we used it for both CONV and RTD because there were insufficient data to try to distinguish the outcome. Also, the patients in these studies are from the general population, rather than the "healthy subpopulation" the military is generally considered to be. Thus, it is possible that *AMedP-7.5* overestimates the time until CONV and RTD for burn patients.

Specifically, the equation for length of hospital stay given by Wong and Ngim is:[519]

$$\begin{aligned}\text{Length of hospital stay (days)} &= 1.93 + 0.93 \times \%BSA + 3.20 \times \text{full thickness } \%BSA + 0.14 \times \text{age} \\ &+ 6.97 \times \text{status of respiratory injury,}\end{aligned} \quad (8)$$

where "status of respiratory injury" equals 0 if there is no respiratory injury and 1 if there is respiratory injury. Table 146 contains results from Equation 8 that are relevant for the insult ranged presented in the MTOR table (Table 148). The average result from the 5% BSA calculations serves as useful confirmation that RTD on Day 15 is a reasonable estimate.

Table 146. Results from Equation 8 Relevant for Derivation of Table 148

% BSA[a]	Age[b]	Respiratory Injury	Length of Hospital Stay (days)	Average	% Difference From Figure 10 Equation[c]
5	25	No	10.05	13.5	24.5
5	25	Yes	17.02		
15	25	No	19.35	22.8	8.1
15	25	Yes	26.32		
25	25	No	28.65	32.1	2.4
25	25	Yes	35.62		
37.5	25	No	40.28	43.8	-1.0
37.5	25	Yes	47.25		
45	25	No	47.25	50.7	-2.2
45	25	Yes	54.22		

Note: Full-thickness %BSA was set to 0 because the *AMedP-7.5* %BSA already includes full-thickness burns. Although this may result in an underestimate of recovery time, we made this choice in part to offset the likely overestimate in recovery time resulting from using an equation derived from the general population instead of the military population.

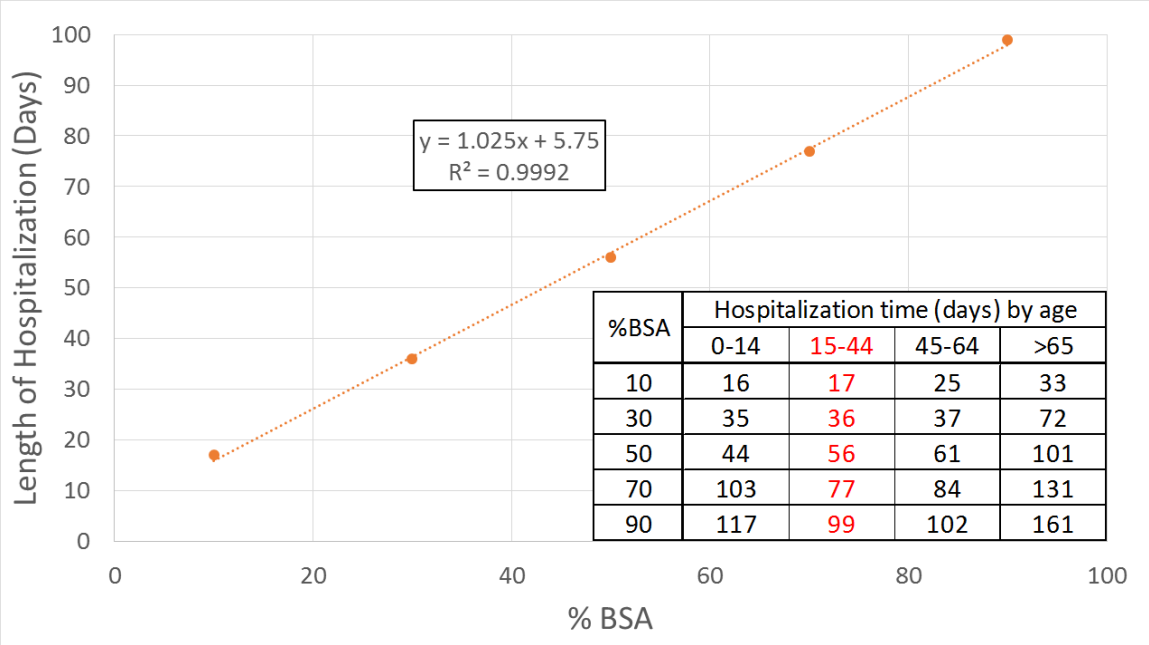
[a] The %BSA values chosen represent either the middle of an insult range, or in the case of the highest range, the bottom value.

[b] The age of 25 was chosen to represent the military population.

[c] Calculated by taking the difference and dividing by the Figure 10 equation's result.

519 Wong and Ngim, "Burns Mortality and Hospitalization Time," 42.

As a check on the other calculated averages, we extracted data from Curreri, Luterman, Braun, and Shires on time of hospitalization as a function of %BSA for the age range 15–44 years[520] and performed a simple fit using only %BSA as a variable (Figure 10). As indicated in Table 146, the difference between the two estimates of time to CONV/RTD is small, particularly beyond 10 %BSA. Since the Wong and Ngim equation better takes into account relevant factors, we used its results to inform the MTOR table. Specifically, the time to CONV or RTD for the insult ranges (other than 1 – <10 %BSA, where time to RTD is based on the Injury Profile) is equal to the "average" value in Table 146 rounded *up* to the next day, to account for *AMedP-7.5*'s reporting rules from Table 15.



%BSA	Hospitalization time (days) by age			
	0-14	15-44	45-64	>65
10	16	17	25	33
30	35	36	37	72
50	44	56	61	101
70	103	77	84	131
90	117	99	102	161

Figure 10. Predicted Hospitalization Time Data from Curreri, Luterman, Braun, and Shires, with Fit by IDA

Since the untreated Injury Profiles (Table 145) indicate death for the ≥30 %BSA insult range, we *assumed* that with medical treatment, those with >30 %BSA would either become CONV or DOW,[521] that those well below 30 %BSA (<20 %BSA) would all become RTD, and that 50% of those in the 20 – <30 %BSA insult range would become CONV and the other 50% RTD. Note that although these decisions are logical, they are arbitrary.

To estimate the fraction that becomes DOW instead of CONV for ≥30 %BSA, we again used an equation provided by Wong and Ngim (Equation 11), the results from which

520 Curreri, Luterman, Braun, and Shires, "Burn Injury," Table 7.

521 The fraction that becomes DOW vice CONV is discussed in the following paragraph.

are shown in Table 147. As noted in Table 147, the final values for the two ≥30 %BSA insult ranges were rounded to one significant digit. The MTOR has two ≥30 %BSA insult ranges because the change in probability of death is significant and we wanted to capture that variability. We created only *one* extra insult range in an attempt to balance useful fidelity against creating an overly complicated model.

$$\text{Probability of death} = \frac{1}{1 + e^{8.32 - 0.15 \times \%BSA - 2.96 \times \text{status of respiratory injury}}} \quad (9)$$

Table 147. Results from Equation 9 Relevant for Derivation of Table 148

% BSA[a]	Respiratory Injury	Probability of DOW	Average	Value Used for *AMedP-7.5*
5	No	0.1	0.5	0[b]
5	Yes	1.0		
15	No	0.2	2.3	0[b]
15	Yes	4.3		
25	No	1.0	8.8	0[b]
25	Yes	16.7		
37.5	No	6.3	31.5	0.3
37.5	Yes	56.6		
45	No	17.2	48.6	0.5
45	Yes	80.1		

[a] The %BSA values chosen represent either the middle of an insult range, or in the case of the highest range, the bottom value.

[b] Values are 0 for consistency with the untreated Injury Profiles, which are intended to show the course for the "median individual"; viewed in this sense, using a value of 0 makes sense.

The final piece of Table 148 that has not been explained is the time to DOW. The value of 9 days is taken from Wong and Ngim, who stated that the median time to death in their 16 patients who died was 9 days.[522]

Table 148. Thermal Fluence Medical Treatment Outcome Reporting

Insult Range (%BSA)	DOW[a]	CONV[a]	RTD[a]
1 – <10	0%	0%	Day 15: 100%
10 – <20	0%	0%	Day 23: 100%
20 – <30	0%	Day 33: 50%	Day 33: 50%
30 – <45	Day 9: 30%	Day 44: 70%	0%
≥45	Day 9: 50%	Day 51: 50%	0%

[a] Reported values indicate the fraction that changes status on a given day; they are not cumulative.

522 Wong and Ngim, "Burns Mortality and Hospitalization Time," Table 1.

Calculation of Effective Insult (*AMedP-7.5 Section 4.4.4.3*)

AMedP-7.5 Equation 4-38 is used to calculate the Effective CBRN Challenge for thermal fluence injuries (%BSA) for personnel. It is derived from a U.S. Defense Nuclear Agency (DNA) study conducted by Levin in the early 1990s.[523] The variant used in *AMedP-7.5* corrects a typographical error made in the original report, described below, and expands the equation to account for the percentage of body covered by a uniform and the percentage of body that is bare.

Under the assumption that there is equal probability that any side of the body will be facing a nuclear detonation, Levin used a cylindrical model of the body to estimate the effective area burned.[524] This underlying concept is shown in Figure 11.

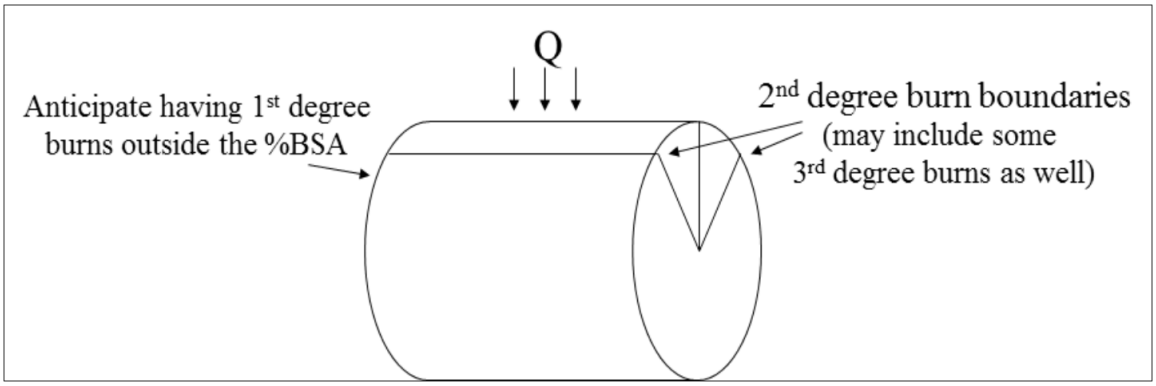


Figure 11. Cylindrical Model for Man Used to Estimate Area Burned from Thermal Fluence

The corresponding equation, which calculates the area burned as a percent of the total area, is shown in Equation 10:

$$\%BSA = {\arccos(Q_t/Q)}/{\pi}, \quad (10)$$

where:

Q_t = the thermal fluence threshold value for a second-degree burn,

Q = the thermal fluence to which the cylinder is exposed

The typographical error in Levin's report was a transposition of Q and Q_t. Because the argument of the arccosine function (expressed in radians) can never be greater than one, it is evident that the two terms are meant to be positioned as shown in Equation 10. Further, a comparison of the numerical values provided by Levin to those calculated using the updated equation confirms that this is how he implemented it in his report.

523 Levin, *Effect of Combined Injuries*.

524 Ibid., 23

The thermal fluence threshold value in Levin's equation, Q_t, varies as a function of clothing type and the extent to which it covers the body. *AMedP-7.5* Table 4-59 provides thermal fluence threshold values corresponding to 50% incidence of second-degree burns for various uniform types. The bare skin value in this table is taken from Levin's report;[525] and all others are taken from a 1986 report from Harry Diamond Labs.[526] Levin's report contains thermal fluence threshold values for selected uniform types as well, and these values are consistent with those found in the Harry Diamond Labs report. Note that the values provided in *AMedP-7.5* are expressed in kJ/m^2 to be consistent with internationally recognized metric units.

In cases where the uniform type does not completely cover the body, the %BSA equation must account for both the injury to bare skin and the injury to clothed skin. To do so, the %BSA equation given above must be calculated once using the bare skin threshold value and once using the uniform threshold value. The output of the equation generated with the bare skin threshold value is then multiplied by the percent of BSA that is bare, while the output generated with the uniform type threshold value is multiplied by the percent of body surface area that is clothed. The results are summed to determine the total %BSA. Implementing this paragraph leads to *AMedP-7.5* Equation 4-38. The recommended values for the percentage of the body covered and not covered by uniform (*AMedP-7.5* footnote 71, on page 4-66) are taken from page 24 of Levin's report.

AMedP-7.5 Table 4-58 reports thermal transmission probabilities for various vehicle and shelter types, which are used to calculate the fraction of an icon that received the Effective CBRN Challenge. *AMedP-7.5* simply states that the values are notional, reflecting the fact that they were derived from "professional judgment" by SMEs during the development of *AMedP-8*(*A*).[527]

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525 Ibid., 24.

526 Baba et al., *Incidence of Skin Burns*, Figure 1 and Table 4.

527 According to an unpublished draft of the documentation of *AMedP-8*(*A*) *Nuclear* retained by IDA.

1.18. Biological Agent Model Framework and Important Biological Agent Technical References (*AMedP-7.5 Chapter 5*)

Introduction

This chapter explains the human response submodels that are the basis of the specific agent/disease models, the associated frameworks for estimating casualties of noncontagious and contagious diseases (including justification of assumptions, limitations, and constraints), and the equations used within each of the frameworks. It also identifies the two most important sources used to directly inform the agent/disease models or that supported model development.

Human Response Submodels (*AMedP-7.5 Section 5.1.1*)

The five submodels described in this section form the framework of the human response models for biological agents. Before the agent-specific parameters can be understood, one must have a general knowledge of how the submodels fit together and how each is characterized. This section will provide a basis for that understanding and allow the reader to more fully comprehend the meaning of the parameters in the following chapters.

The human response portion of the casualty estimation methodologies, which comprise the five submodels, requires only one input: the dose of inhaled agent associated with each icon (i.e., a group of individuals who share a common location over time), which in the context of *AMedP-7.5* is more generically referred to as the Effective CBRN Challenge. Using this value, the five submodels are employed as shown in Figure 12 to determine (1) the number of individuals expected to become ill; (2) the number of individuals expected to die; (3) the time between exposure and the onset of signs and symptoms of illness; (4) the severity of these signs and symptoms over time; and (5) finally the time at which the signs and symptoms change and the patient dies, becomes convalescent, or fully recovers.

15. Infectivity/Effectivity

The first human response submodel, called the infectivity submodel for replicating organisms (viruses, bacteria, rickettsiae) and the effectivity submodel for toxins, is used to estimate the number of individuals that become clinically ill as a function of inhaled dose. This portion of the human response methodology defines the likelihood of an exposed individual becoming infected/affected *and* clinically ill. Individuals who are subclinically infected/affected but who never exhibit signs and symptoms of illness will not present to the medical system and are excluded from the models.[528] Depending on the available data, the infectivity/effectivity submodel may be characterized as a dose-dependent probability

[528] The exclusion of subclinical infections and effects is accomplished by excluding data on subclinical infections and effects from the derivation of infectivity/effectivity parameters.

distribution or as a threshold dose at or above which all (and below which no) individuals become ill.

If pre-exposure prophylaxis is effective in preventing infection with a particular agent or post-exposure prophylaxis is effective in aborting a nascent infection with a particular agent, these effects can be incorporated into the infectivity/effectivity submodel. The method by which prophylaxis has been incorporated into the existing models is to use a multiplier that that reduces the size of the population at risk (PAR). For example, if a vaccine were 95% effective in preventing illness, then the infectivity/effectivity calculation would be applied to only 5% of the vaccinated, challenged individuals. The rest of the vaccinated, challenged individuals would be fully protected. However, if supporting data were to indicate some other way of modeling the effects of prophylaxis (e.g., including a "defeat dose" beyond which the prophylaxis is ineffective, as with chemical agents), the models would be made accordingly.

Because medical treatment, by definition, does not occur until after symptoms have appeared, the untreated and treated human response models always use the same infectivity/effectivity submodel.

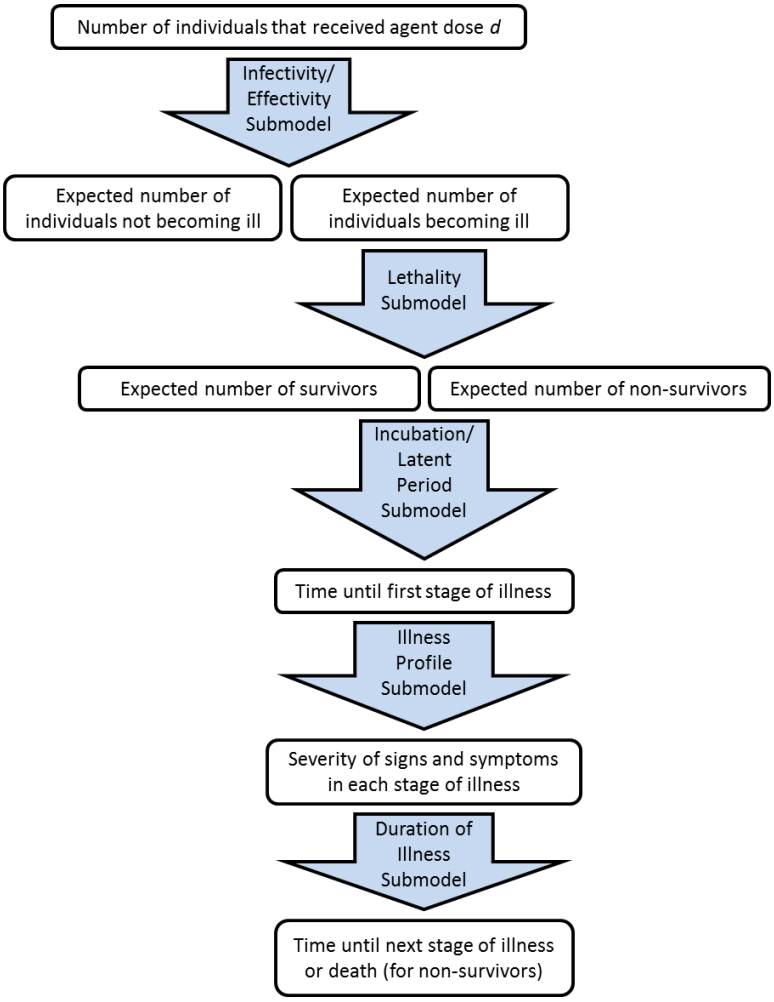

Figure 12. Biological Agent Human Response Submodel Overview

16. Lethality

For untreated models, the lethality submodel estimates the number of ill individuals that become fatalities in the absence of treatment and is designed to be flexible enough to account for the different ways that the probability of death is defined in the literature. Typically, lethality is characterized with a CFR (conditional probability of death given illness or the fraction of ill individuals that die) or as a dose-dependent probability of death.[529] Both these forms of expressing lethality following biological agent exposure are acceptable, and the available data inform the decision of which to choose. The chosen representation dictates the method of implementation to determine the number of individuals expected to die.

529 For both methods of defining probability of lethality, the reality is that other factors such as age, sex, weight, and co-morbidity may also matter. However, because the available data typically do not address these dependencies, the models presented in this document also do not address them.

To avoid the case where the expected number of fatalities exceeds the expected number of ill individuals, the dose-dependent probability of lethality must be less than or equal to the probability of infectivity/effectivity for all doses. On the other hand, the conditional probability of death given illness is not constrained by the probability of infectivity/effectivity and may range from 0% to 100%. Depending on the details of the disease and the effects of available medical treatment options, the untreated and treated lethality models may differ or may be identical.

17. Incubation/Latent Period

Biological agents typically cause diseases that manifest signs and symptoms as late as many days after exposure. The duration of time between exposure and the onset of signs and symptoms is the incubation period (or latent period for toxins). The incubation/latent period submodel is used to estimate the number of individuals progressing through this asymptomatic period and entering the first stage of illness (at which time signs and symptoms initially manifest) on each day.

The incubation/latent period may or may not depend on the dose. In either situation, the submodel is ideally characterized by a continuous probability density function that can be used to calculate the probability of becoming symptomatic at a specified elapsed time post-exposure. If limited data are available, a constant latent period may be assumed.

Because the incubation/latent period, by definition, occurs before the onset of symptoms, the untreated and treated human response models always use the same incubation/latent period submodel.

18. Injury Profile

The Injury Profile submodel translates the qualitative aspects of a disease (the severity of illness over time) into a quantitative representation useful for estimating casualties. Derived from clinical descriptions of a disease, the Injury Profile is characterized by one or more illness stages, each with a unique combination of signs and symptoms correlated to an Injury Severity Level.

In practice, the signs and symptoms of a disease over time dictate the number of stages in the Injury Profile. For instance, if the typical course of a particular disease progressed from one sign and symptom complex to a markedly different combination of signs and symptoms to complete recovery, then the Injury Profile would reflect this progression by dividing the disease into two stages: one categorized by the first set of signs and symptoms and one characterized by the second set.

The Injury Severity Level scale shown in Table 2 is used to rate the signs and symptoms in each stage of illness. Depending on the details of the disease and the effects of available medical treatment options, the untreated and treated Injury Profiles may differ or may be identical.

19. Duration of Illness

At a minimum, the duration of illness is characterized by an estimate of the total time between sign and symptom onset and either death or the cessation of signs and symptoms. To capture some of the variability in the duration of illness, a continuous probability distribution defining the probability of completing the disease as a function of time can be used to represent the total symptomatic period. If additional data are available to characterize the duration of time spent in each stage of illness and if the times spent in each stage of illness are assumed to be independent variables, then it is possible to model each stage of illness using a separate probability distribution. If no data exist to support modeling each stage of illness on its own, one probability distribution can describe the total duration of illness, and individuals can be assumed to spend an equal (or some other proportional) amount of time in each of the stages. If insufficient data are available to develop a probabilistic model, constant duration of illness models can also be used.

Outputs from the untreated duration of illness submodel include the numbers of individuals that are expected to enter each stage of illness (other than the first, which is dictated by the incubation/latent period model) for each day and the daily number of DOW and RTD casualties. The treated model also reports the daily number of CONV casualties. Depending on the details of the disease and the effects of available medical treatment options, the untreated and treated duration of illness models may differ or may be identical, apart from the difference in reporting CONV.

Challenges Associated with Deriving Submodel Parameter Values

The common challenge associated with developing parameter values for all five submodels is finding high-quality data. For infectivity/effectivity of lethal agents, estimates are often based on animal data because controlled human exposure is not feasible. For naturally occurring diseases, the lethality and incubation period models are usually based on human data from specific outbreaks or cases, which may not be representative but are all that is available in the literature. For incubation period, a further complication for naturally occurring cases is that the time of exposure is not necessarily known with high precision or confidence. Even duration of illness data can suffer from low precision data, since the exact day on which symptoms appeared is not always clear to patients when they report to the hospital days later. Specific issues for each submodel and each agent are discussed in the agent-specific chapters.

Assumptions and Limitations (*AMedP-7.5 Section 5.1.3*)

Assumption: All challenges relate to inhalation of the aerosolized agent.

Many of the biological agents considered in *AMedP-7.5* can cause disease via a number of different routes of entry: inhalation, ingestion, ocular exposure, or cuts and abrasions. Biological model parameter values generally vary by route of entry. For the agents considered, aerosol dissemination would have the greatest potential to cause large numbers of casualties and thus pose the greatest challenge to the medical system. For this reason, the parameter values associated with the inhalation route of entry were chosen.

Assumption: The efficacy of prophylaxis and medical treatment are independent of the dose; no "defeat dose" exists.

Although this may not be true in some cases, data on defeat doses are typically unavailable. Further, defeat doses are likely sufficiently high that this assumption will have a negligible effect on the accuracy of the model.

Assumption: A CFR of 1% or below is negligible; a CFR of 0% will be used. Similarly, in the absence of a well-quantified CFR, 0% or 100% lethality is used in place of qualitative descriptions such as "highly lethal without treatment" or "rarely fatal."

AMedP-7.5 is a *planning* tool, and such small percentages will have little effect on the overall planning; therefore, they should be ignored for the sake of simplicity of the model.

Assumption: Because of the relatively long incubation/latent periods and durations of illness (as compared to the time required to reach an MTF), biological agents will not cause KIAs.

Sufficient explanation is provided in *AMedP-7.5*.

Assumption: The period during which an individual is ill can be subdivided into one or more stages, and Injury Severity Levels related to signs and symptoms can be associated with these stages.

The purpose of this assumption is to allow for resolution in time and severity of injury beyond simply stating that a person is ill. Thus, it fits naturally with the Injury Severity Level scale defined in Table 2 and with the basic concept of providing a time-resolved casualty estimate. In other words, this assumption is an essential part of the methodology.

Limitation: The methodology uses population-based estimates of injury severity over time. Thus, the casualty category of a particular icon *cannot* be tracked over time.

Because the biological agent human response methodologies rely on probability distributions, the results are captured over the entire population rather than on an individual basis.

> **Limitation**: The infectivity models were derived such that the methodology ignores "subclinical" infections; everyone who is "infected" will become symptomatic. Likewise, the effectivity models were derived such that the "effect" is the onset of signs and symptoms.

Essentially this means that subclinical infections are ignored, which is consistent with the concept that *AMedP-7.5* is a symptom-based methodology. This should have no effect on the accuracy of the casualty estimates.

Important Biological Agent Technical References (*General Information Related to AMedP-7.5 Sections 5.2.1 through 5.2.18*)

At the outset of the search for data to inform model development, we identified two particularly relevant and useful references. This section briefly describes these references and explains their role in the development of the models of human response for the five biological agents. Together, these documents provided a useful overview of the human response to each agent and served as a starting point for gathering the relevant underlying data. We also used a number of other sources for each agent, as cited in the agent-specific chapters.

20. *Medical Aspects of Biological Warfare* (*MABW*)

This volume[530] in the Textbooks of Military Medicine series contains chapters on all of the agents discussed in this TRM. The chapters provide information on clinical manifestations of exposure, medical treatment, recovery, and general information on the use of these agents as biological weapons. Our main use of the chapters was to identify authoritative sources of original data and as a source of qualitative confirmation that the derived parameters are consistent with prior knowledge; however, these chapters also occasionally directly informed the parameterization.

21. *Medical Management of Biological Casualties Handbook* (*MMBC*)

This publication[531] from the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) provides general overviews of the clinical manifestations of the agents, medical treatment, and recovery, and general information on the use of each agent as a weapon. When no other data were available, we used information provided in this document to directly inform the submodel parameterization. Other information confirmed

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530 Zygmunt F. Dembek, ed., *Medical Aspects of Biological Warfare*, Textbooks of Military Medicine (Washington, DC: Department of Defense, Office of the Surgeon General, U.S. Army, Borden Institute, 2007).

531 U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID), *Medical Management of Biological Casualties Handbook*, 7th ed., ed. Zygmunt F. Dembek (Fort Detrick, MD: USAMRIID, September 2011).

parameters generated from other data. Unless specifically noted otherwise, every reference in this document to *MMBC* refers to the seventh edition.

The *AMedP-8* (*Biological*) *Methods Report* (*P-8 BMR*)

This report, as stated on its second page, "describes the background and methods used to generate data and tables for Allied Medical Publication 8 (AMedP-8), the Medical Planning Guide for the Estimation of NBC Battle Casualties, Volume II (Biological)."[532] In essence, it is a summary of the work conducted to develop a previous version of the AMedP-8 biological agent methodology. The same types of information needed for the previous version are needed for *AMedP-7.5*, so the *P-8 BMR* is a valuable resource despite our disagreement on some of the parameter values.

Non-Contagious Casualty Estimation (*AMedP-7.5 Sections 5.1.4*)

AMedP-7.5 Figure 5-1 depicts how the five human response submodels are combined to generate the casualty estimate. The infectivity/effectivity (including prophylaxis, where relevant) and lethality models provide inputs to *AMedP-7.5* Equations 5-1 to 5-4; these four equations are either sufficiently explained in *AMedP-7.5* or sufficiently self-explanatory that no more discussion is warranted here. The incubation/latent period, Injury Profile, and duration of illness models were combined to generate Probability Density Tables (PDTs) for each agent. The Subsections of *AMedP-7.5* Section 5.2 provide direction for using the casualty criterion and PDTs with the results of *AMedP-7.5* Equations 5-1 to 5-4 to generate the casualty estimate. Since everything else is sufficiently explained in *AMedP-7.5*, this section will focus on describing how the PDTs were generated.

The first step in developing PDTs for a disease is to convolute the incubation/latent period model with the duration of illness model (which may comprise several parts). Since most of the models are stochastic, one option is to use a Monte Carlo simulation,[533] which employs a number of random draws—taken from each distribution sequentially and then summed—until the confidence interval (error bars) of the estimate converge to a sufficiently small number. Alternatively, this can be approximated through the use of a convolution algorithm wherein each distribution is represented by fractional values at discrete time steps to approximate the continuous function.[534] These discrete distributions are then combined using matrix multiplication. Thus, the time to the end of a stage of illness is represented by numerically convolving (or performing matrix multiplication on) the

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532 George H. Anno et al., *Biological Agent Exposure and Casualty Estimation: AMedP-8* (*Biological*) *Methods Report*, GS-35F-4923H (Fairfax, VA: General Dynamics Advanced Information Systems, May 2005), 2.

533 In general, the Monte Carlo method defines a domain of possible inputs, generates inputs randomly from the domain using a certain specified probability distribution, performs a deterministic computation using the inputs, and aggregates the results of the individual computations into a final result.

534 E. Oran Brigham, *The Fast Fourier Transform and Its Applications* (Englewood Cliffs, NJ: Prentice Hall, 1988), 118.

fraction of population first manifesting symptoms by day (the incubation/latent period submodel) with the fraction of population progressing from Stage 1 to Stage 2 of illness (the Stage 1 duration of illness submodel)—this can be extended for any number of stages of illness. Likewise, the time to DOW, CONV, or RTD may be represented by convolving the incubation/latent period submodel with all relevant stages of the duration of illness submodel. This process, as implemented to generate the PDTs for *AMedP-7.5*, is described in detail below.

For a given distribution (e.g., incubation/latent period, duration of illness), the cumulative distribution function (CDF), denoted $F(t)$, is evaluated to estimate the cumulative percentage of individuals completing the corresponding stage of disease by time t. The percentage of individuals completing that disease stage in the span of time Δt preceding t is calculated using Equation 11.

$$F(t) - F(t - \Delta t) \tag{11}$$

More specifically, the percentage of individuals completing the incubation period in the ith time span of duration Δt after becoming infected, denoted $Inc(i)$, is estimated from the incubation period CDF F_{inc} by evaluating Equation 12.

$$Inc(i) = F_{inc}(i\Delta t) - F_{inc}(i\Delta t - \Delta t) \tag{12}$$

Similarly, as shown in Equation 13, the percentage of individuals completing the first stage of illness in the ith time span of duration Δt after completing the incubation period, denoted $Stg1(j)$, is estimated from the CDF of the duration of illness model for this stage, F_{Stg1}.

$$Stg1(j) = F_{Stg1}(j\Delta t) - F_{Stg1}(j\Delta t - \Delta t) \tag{13}$$

Given these two equations, it is possible to estimate, at any given time, the percentage of individuals having completed both the incubation period and the first stage of illness. Consider the case where Δt = 1 day and the percentage of individuals having completing both stages by Day 3 ($F_{IncStg1}(3)$) is sought. This is computed by summing the percentage finishing the incubation period in 1 day ($Inc(1)$) and the first stage of illness in 1 day ($Stg1(1)$), the percentage finishing the incubation period in 1 day ($Inc(1)$) and the first stage of illness in 2 days ($Stg1(2)$), and the percentage finishing the incubation period in 2 days ($Inc(2)$) and the first stage of illness in 1 day ($Stg1(1)$). Mathematically, this can be expressed as shown in Equation 14.

$$F_{IncStg1}(3) = Inc(1) \times Stg1(1) + Inc(1) \times Stg1(2) + Inc(2) \times Stg1(1) \tag{14}$$

One shortcoming of using this technique when Δt is limited to whole days is that no other combination of disease stage durations can result in individuals progressing through

the first stage of disease in 3 days. Consequently, $F_{IncStg1}$ is better approximated when Δt is reduced, allowing individuals to spend fractions of a day in a given stage. Although Δt may be as small as desired, to report results by day, it must divide evenly into 1 day; for the convolutions used in *AMedP-7.5*, Δt = 0.01 days.

When described more generally, Equation 14 represents a numerical approximation of the CDF of the convolved distributions. This more general description, shown as Equation 15, was used to determine the percentage of individuals having progressed through both the incubation period and the first stage of illness by the end of the nth time span of duration Δt after becoming infected.

$$F_{IncStg1}(n) = \sum_{x=2}^{n}\left(\sum_{y=1}^{x-1} Inc(y) \times Stg1(x-y)\right) \tag{15}$$

For reporting purposes, only the daily percentages of individuals finishing a given stage are needed. Thus, to determine the percentage of individuals finishing the first stage of illness on Day D (after having already progressed through the incubation period), Equation 15 was evaluated at the two values of n corresponding to D and $D-1$, and the difference between the two evaluations was taken, as shown in Equation 16, where x is defined as the number of time periods in 1 day ($x\Delta t = 1$).

$$G_{IncStg1}(D) = F_{IncStg1}(Dx) - F_{IncStg1}\big((D-1)x\big) \tag{16}$$

To similarly convolve the distributions of any subsequent stages of illness, the distributions were expressed as the difference between evaluations of the CDF at times separated by any arbitrary time span Δt. This is shown in Equation 17 for the convolved distribution approximated by Equation 15, where the percentage of individuals completing both the incubation period and the first stage of illness in the nth time span of duration Δt after becoming infected is denoted $IncStg1(n)$.

$$IncStg1(n) = F_{IncStg1}(n) - F_{IncStg1}(n-1) \tag{17}$$

The general pattern of these equations can be extended to any number of sequential stages of disease—*AMedP-7.5* disease models have as many as four stages of disease. In this manner, discrete approximations of the distributions for each of the time-based submodels were developed to define the fractions of the population experiencing various milestones in the course of illness on each day. A Microsoft Excel spreadsheet with embedded Visual Basic for Applications code was created to perform the convolutions.

The spreadsheet can handle up to four stages of sequential illness following the incubation/latent period. The spreadsheet can be made available upon request.[535]

Injury Profiles determine how to *label* each PDT (and how/where each PDT reference fits in the disease-specific flowcharts at the end of each subsection of Section 5.2). For example, if the Injury Profile says that Stage 1 of Disease X is Injury Severity Level 2, then the PDT related to the time at which individuals enter Stage 1 of Disease X will be titled "Daily Fraction of Individuals Ill with Disease X Who Become WIA, for Casualty Criterion WIA(1^+) or WIA(2^+)." If Stage 1 of Disease X was Injury Severity Level 1, then "or WIA(2^+)" would be removed from the title, and if Stage 1 of Disease X was Injury Severity Level 1, then the title would end at "Who Become WIA," since there would then be no casualty criterion that could prevent someone in Stage 1 of Disease X from becoming WIA.

Note that the reporting rules from Table 15 also apply to biological agents. Adherence to these rules is the basis for the difference between *AMedP-7.5* Equation 5-5 and 5-6 and between *AMedP-7.5* Equation 5-7 and 5-8. Other facets of these equations are sufficiently explained in *AMedP-7.5* or sufficiently self-explanatory such that no further explanation is warranted here.

Contagious Casualty Estimation (*AMedP-7.5 Section 5.1.5*)

SEIRP Model Equations

This section focuses on explaining the construction of *AMedP-7.5* Equations 5-9 through 5-31, which are the finite-difference equations used to determine the populations of the SEIRP model cohorts on different days. Given this relatively narrow focus, it is particularly important that the reader be familiar with the content of *AMedP-7.5* Section 5.1.5 before reading the remainder of this section.

Equation 5-9:	fraction of icon that received efficacious prophylaxis; sum across all icons
Equation 5-10:	fraction of the icon that did not receive efficacious prophylaxis, multiplied by the probability of illness for the same icon; sum across all icons
Equation 5-11:	simple arithmetic, given that P and E are known for Day 0 (on Day 0, only the P, E, and S cohorts can have non-zero population)

535 The exchange would have to be facilitated by the CBRN Staff Officer in the U.S. Army Office of the Surgeon General/MEDCOM, G-37 Force Management, Defense Health Headquarters, 7700 Arlington Blvd, Falls Church, VA 22042. This individual has historically been the Head of Delegation to the CBRN Medical Working Group and BioMedical Panel meetings. It may be easiest to first email Dr. Sean Oxford, soxford@ida.org, who was the primary Institute for Defense Analyses researcher responsible for *AMedP-7.5* and this TRM.

Equation 5-12:

$$P(d) = P(d\text{-}1) \cdot \left(1 - \nu_{off}(d\text{-}1)\right) + \nu_{on}(d\text{-}1) \cdot \left(\rho_S \cdot S(d\text{-}1) + \rho_E(d_{p\text{-}on}) \cdot E(d\text{-}1)\right)$$

End of antibiotic prophylaxis; Start of prophylaxis; Moving from S to P; Moving from E to P

Equation 5-13:

$$S(d) = S(d\text{-}1) \cdot \left(1 - \rho_S \cdot \nu_{on}(d\text{-}1)\right) \cdot \left(1 - \frac{\beta(d\text{-}1) \cdot \left(\alpha \cdot I_1(d\text{-}1) + (1\text{-}\alpha) \cdot I_2(d\text{-}1)\right)}{N_0}\right) + \nu_{off}(d\text{-}1) \cdot P(d\text{-}1)$$

Moving from S to P when prophylaxis starts; I_1 causes S to move to E; I_2 causes S to move to E; Moving from P to S when prophylaxis ends

Equation 5-14: a fraction of E_1 moves to P based on the efficacy of prophylaxis and when prophylaxis starts

Equation 5-15: by definition, E_2 is zero on all days less than the duration of E_1

Note: if the duration of E_1 is an integer, Equations 5-16 and 5-17 are used; if it is not, the equations are not used because d increases in integer steps

Equation 5-16: by definition, the population of E_1 is zero on the day equal to the duration of E_1

Equation 5-17: all personnel who were in E_1 on Day d-1 move to E_2 on Day d, unless they received effective prophylaxis on Day d-1 (in which case they move to P)

Equation 5-18:

$$E_1(d) = E_1(d\text{-}1) \cdot \left(1 - \rho_E(d_{p\text{-}on}) \cdot \nu_{on}(d\text{-}1)\right) \cdot \left(1 - \frac{1}{\mu_{E1}}\right) + \frac{S(d\text{-}1) \cdot \left(1 - \rho_S \cdot \nu_{on}(d\text{-}1)\right) \cdot \beta(d\text{-}1) \cdot \left(\alpha \cdot I_1(d\text{-}1) + (1\text{-}\alpha) \cdot I_2(d\text{-}1)\right)}{N_0}$$

Moving from E to P when prophylaxis starts; Moving from E_1 to E_2 based on incubation period; I_1 causes S to move to E; I_2 causes S to move to E; New E created by contagious spread from I to S; Moving from S to P when prophylaxis starts; Population of S eligible to be infected by I

Equation 5-19:

$$E_2(d) = E_2(d\text{-}1) \cdot \left(1 - \rho_E(d_{p\text{-}on}) \cdot \nu_{on}(d\text{-}1)\right) \cdot \left(1 - \frac{1}{\mu_{E2}}\right) + \frac{E_1(d\text{-}1) \cdot \left(1 - \rho_E(d_{p\text{-}on}) \cdot \nu_{on}(d\text{-}1)\right)}{\mu_{E1}}$$

Moving from E to P when prophylaxis starts; Moving from E_2 to I_1 based on incubation period; Moving from E_1 to E_2 based on incubation period; those moving to P first removed

Equation 5-20:

$$I_1(d) = \left(I_1(d-1) \cdot \left(1 - \frac{1}{\mu_1}\right) + \frac{E_2(d-1) \cdot \left(1 - \rho_E(d_{p\text{-}on}) \cdot \nu_{on}(d-1)\right)}{\mu_{E2}} \right) \cdot (1 - MT_{on}(d) \cdot MT_{I1} \cdot WIA_{I1})$$

Moving from I_1 to I_2 based on duration of illness

Moving from E_2 to I_1 based on incubation period; those moving to P first removed

Moving from I_1 to R_S if WIA and receiving treatment that eliminates contagiousness

Equation 5-21:

$$I_2(d) = I_2(d-1) \cdot \left(1 - \frac{1}{\mu_2}\right) + \frac{I_1(d-1)}{\mu_1}$$

Moving from I_2 to R based on duration of illness

Moving from I_1 to I_2 based on duration of illness

Equation 5-22:

$$R_{DOW}(d) = R_{DOW}(d-1) + \frac{I_2(d-1)}{\mu_2} \cdot p_f(d-1)$$

Fraction leaving I_2 that dies and therefore enters R_{DOW}

Equation 5-23:

$$R_S(d) = R_S(d-1) + \frac{I_2(d-1)}{\mu_2} \cdot \left(1 - p_f(d-1)\right) - \frac{I_2\left(d-(1+\mu_{RS})\right)}{\mu_2} \cdot \left(1 - p_f\left(d-(1+\mu_{RS})\right)\right)$$
$$+ (MT_{on}(d) \cdot MT_{I1} \cdot WIA_{I1}) \cdot \left(I_1(d-1) \cdot \left(1 - \frac{1}{\mu_1}\right) + \frac{E_2(d-1) \cdot \left(1 - \rho_E(d_{p\text{-}on}) \cdot \nu_{on}(d-1)\right)}{\mu_{E2}} \right)$$
$$- \left(MT_{on}(d-\mu_{RS}) \cdot MT_{I1} \cdot WIA_{I1}\right)$$
$$\cdot \left(I_1\left(d-(1+\mu_{RS})\right) \cdot \left(1 - \frac{1}{\mu_1}\right) + \frac{E_2\left(d-(1+\mu_{RS})\right) \cdot \left(1 - \rho_E(d_{p\text{-}on}) \cdot \nu_{on}\left(d-(1+\mu_{RS})\right)\right)}{\mu_{E2}} \right) \text{¤}$$

Fraction leaving I_2 that survives and therefore enters R_S…

…same personnel leaving R_S and going to R_{RTD} after completing recovery

Entire population of I_1 moves to R_S if WIA and receiving treatment that eliminates contagiousness…

…same group leaves R_S when treatment ends, enters R_{RTD}

Equation 5-24:

$$R_{RTD}(d) = R_{RTD}(d\text{-}1) + \overbrace{\frac{I_2\left(d\text{-}(1+\mu_{RS})\right)}{\mu_2} \cdot \left(1 - p_f\left(d\text{-}(1+\mu_{RS})\right)\right)}^{\text{Survivors that left } I_2\text{, entered } R_S\text{, and now leave } R_S \text{ to enter } R_{RTD}}$$

$$\underbrace{+ \left(MT_{on}\left(d\text{-}\mu_{RS}\right) \cdot MT_{I1} \cdot WIA_{I1}\right) \cdot \left(I_1\left(d\text{-}(1+\mu_{RS})\right) \cdot \left(1 - \frac{1}{\mu_1}\right) + \frac{E_2\left(d\text{-}(1+\mu_{RS})\right) \cdot \left(1 - \rho_E(d_{p\text{-}on}) \cdot \nu_{on}\left(d\text{-}(1+\mu_{RS})\right)\right)}{\mu_{E2}} \right)}_{\text{Population of } I_1 \text{ that moved to } R_S \text{ due to treatment that eliminates contagiousness, and now moves to } R_{RTD} \text{ because treatment ends}}$$

Equation 5-25:

$$I_{1,new}(d) = \overbrace{\left(\frac{E_2(d\text{-}1) \cdot \left(1 - \rho_E(d_{p\text{-}on}) \cdot \nu_{on}(d\text{-}1)\right)}{\mu_{E2}} \right)}^{\text{Fraction of } E_2 \text{ moving to } I_1 \text{ based on incubation period; those moving to P first removed…}} \overbrace{\cdot \left(1 - MT_{on}(d) \cdot MT_{I1} \cdot WIA_{I1}\right)}^{\text{…unless they instead go to } R_S \text{ because they received medical treatment that eliminates contagiousness}}$$

Equation 5-26: those leaving I_1 after completing the duration of illness for Stage 1

Equation 5-27:

$$WIA(3)_{spox}(d) = WIA(3)_{spox}(d\text{-}1) \cdot \overbrace{\left(1 - \frac{1}{\mu_2}\right)}^{\text{Moving from } I_2 \text{ to } R_{RTD} \text{ based on duration of illness}} + I_{2,new}(d) \cdot \overbrace{\left(1 - p_f(d\text{-}1)\right)}^{\text{Fraction of those entering Stage 2 that will survive}}$$

Equation 5-28:

$$WIA(4)_{spox}(d) = WIA(4)_{spox}(d\text{-}1) \cdot \overbrace{\left(1 - \frac{1}{\mu_2}\right)}^{\text{Moving from } I_2 \text{ to } R_{DOW} \text{ based on duration of illness}} + I_{2,new}(d) \cdot \overbrace{p_f(d\text{-}1)}^{\text{Fraction of those entering Stage 2 that will not survive}}$$

Equation 5-29: since personnel cannot leave R_{DOW}, the "new" can be calculated by simply using the difference between two consecutive days

Equation 5-30:

$$R_{S,new}(d) = \overbrace{\frac{I_2(d\text{-}1)}{\mu_2} \cdot \left(1 - p_f(d\text{-}1)\right)}^{\text{Survivors moving from } I_2 \text{ to } R_S \text{ based on duration of illness}}$$

$$+ \underbrace{\left(MT_{on}(d) \cdot MT_{I1} \cdot WIA_{I1}\right)}_{I_1 \text{ cohort moves to } R_S \text{ if receiving medical treatment that eliminates contagiousness…}} \cdot \left(\underbrace{I_1(d\text{-}1) \cdot \left(1 - \frac{1}{\mu_1}\right)}_{\text{…but those who completed Stg1 are first removed…}} + \underbrace{\frac{E_2(d\text{-}1) \cdot \left(1 - \rho_E(d_{p\text{-}on}) \cdot \nu_{on}(d\text{-}1)\right)}{\mu_{E2}}}_{\text{…and those completing incubation and entering Stg1 are added}} \right)$$

Equation 5-31: since personnel cannot leave R_{RTD}, the "new" can be calculated by simply using the difference between two consecutive days

Assumptions, Limitations, and Constraints

Assumption: The population is large and unstructured.

The assumption that the population is large allows it to be modeled with parameters derived from real-world regional or metropolitan outbreaks. The assumption that the population is unstructured means the population can be modeled as a single "unit," without ascribing different behaviors or conditions to any subset of the population. Thus, the populations used for casualty estimation should reflect this assumption; that is, the model is not applicable to collections of geographically separated military units.

Assumption: The population mixes homogeneously.

This assumption follows from the unstructured assumption above. All persons have an equal likelihood of mixing with any other person—no subgroup is separated out as more or less likely to mix in the general population. Again, the populations used for casualty estimation should reflect this assumption. Including remote or isolated units with limited contact among the rest of the population (i.e., those entered into the medical system) may result in an overestimate of the number of casualties or an early estimate of when those casualties might occur.

Assumption: Initial and transmission-caused infections follow the same course of disease.

This assumption allows for a simplification and generalization of complex disease processes and permits the practical estimation of the severity and time of biological casualties. Essentially, this assumption implies that the methodology does not consider possible variations in the presentation of a particular disease. Since alternative presentations of a disease may be more or less severe than what is modeled, this assumption may result in an under- or overestimate of the severity of the casualties.

Assumption: The epidemiological circumstances of the historical outbreaks from which the time-varying rate of disease transmission (β(d)) was derived are similar to the circumstances in scenarios of interest to the user.

"Epidemiological circumstances are conditions, facts, and events that form the context or frame of reference for an outbreak of contagious disease. Some epidemiological circumstances facilitate disease transmission and others impede it."[536] This assumption allows the β(d) values to be used. Since no future outbreak will perfectly reflect the epidemiological circumstances for the outbreak from which the β(d) values were derived,

536 John N. Bombardt, *Primary Pneumonic Plague Transmission and BW Casualty Assessments*, IDA Paper P-3657 (Alexandria, VA: Institute for Defense Analyses, December 2001), 38.

there will always be error in the β(d) values. The magnitude of that error cannot readily be quantified, but is proportional to the differences in epidemiological circumstances.

> **Assumption**: Individuals who become WIA, survive the illness (with or without medical treatment), and RTD gain immunity to the disease. Therefore, they do not re-enter the S cohort upon becoming RTD.

This assumption reflects reality in most cases—most people really do become immune to diseases they have survived, at least for the relatively short period of time for which *AMedP-7.5* is to be used. Though immunity may fade over years, *AMedP-7.5* is not intended to be used for predicting the course of outbreaks that last for years.

> **Limitation**: Because the post-exposure prophylaxis efficacy of the smallpox vaccine decreases with time since exposure, and because this SEIRP model is unable to track the time each individual has spent in the E cohort, the day on which prophylaxis is applied is best limited to days before transmission of disease from the I cohort to the S cohort has occurred (to minimize error).

Correctly implementing a time-dependent post-exposure prophylaxis efficacy model would require knowledge of the time each individual has spent in the E cohort prior to incubation, but the SEIRP model as implemented cannot track information about individuals. This only causes error if post-exposure prophylaxis is not applied until after a second generation of individuals begins entering the E cohort—the modeled efficacy for the second (or higher) generation individuals will be artificially lower than it should be, resulting in an overestimate of the number of casualties. This is one of several issues that could be fixed by a rebuilt epidemic model we suggest be created for the next version of *AMedP-7.5*.

> **Constraint**: Because the model uses only mean times (and not standard deviations) to represent the lengths of the incubation period and each stage of illness, it represents all probability distributions as exponential distributions.

This constraint is an artifact of mathematical simplifications made to make the model less complex. The degree of error introduced depends on the difference between the exponential distribution and the proper form of the distribution as listed in *AMedP-7.5* Tables 5-50 and 5-79.

> **Constraint**: The model uses finite-difference equations instead of differential equations and integrals (this introduces some unknown degree of inaccuracy).

This constraint also reflects mathematical simplification of the model.

Equations Needed to Execute Biological Casualty Estimates (*AMedP-7.5 Section 5.1.6*)

AMedP-7.5 Equation 5-32 is a straightforward calculation of probability of "response" as a function of dose, based on probit analysis[537] and the associated fitted parameters for a lognormal distribution. Likewise, *AMedP-7.5* Equation 5-33 is a straightforward implementation of a threshold model. Finally, the form of *AMedP-7.5* Equation 5-34 (linear) also straightforward.

Note that the *reason* a given agent/disease model uses a lognormal distribution, threshold model, linear model, or any other type of model is explained in the chapter for that agent/disease later in this TRM, as are the specific parameter values fed into the equations.

537 Tallarida, "Quantal Dose-Response Data."

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1.19. Anthrax Model
(*AMedP-7.5 Section 5.2.1*)

Introduction

Anthrax is a zoonotic disease caused by *Bacillus anthracis*, a rod-shaped, gram-positive sporulating organism, the spores of which constitute the usual infective form. It occurs worldwide in wild and domesticated animals, primarily herbivores. In humans, the disease is acquired primarily through contact with infected animals or animal products, usually via the cutaneous route. However, anthrax can also be acquired through ingesting or inhaling anthrax spores. The presentation and severity of the disease varies by route of entry: cutaneous anthrax, the most common naturally occurring form of the disease, has a mortality rate of less than 1%, while inhalation anthrax has a mortality rate approaching 100% in the absence of treatment, and even with treatment, mortality rates have historically been between 45% and 70%.[538]

Anthrax acquired via inhalation begins with nonspecific symptoms of febrile illness, including malaise, fatigue, myalgia, and fever; this early phase of the disease continues for a few days. During this period of active infection, anthrax bacteria produce copious amounts of toxin, which circulates in the body and builds up in pleural fluid around the lungs, severely inhibiting respiration. The second, fulminate stage of the disease begins abruptly, with the patient experiencing sudden respiratory distress. In the absence of treatment, there is rapid progression to shock and death, typically within 1 to 2 days.

Assumptions and Limitation (*AMedP-7.5 Section 5.2.1.2*)

> **Assumption**: The disease resulting from exposure to *B. anthracis* is inhalation anthrax.

This assumption is consistent with the assumption of aerosol dissemination that is one of the core assumptions of *AMedP-7.5*.

> **Assumption**: Untreated inhalation anthrax is 100% lethal.

See Subsection 0.

> **Limitation**: Although the model requires the user to specify a day on which antibiotic treatment becomes available ($d_{trt\text{-}anth}$), it does *not* apply treatment

538 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. The mortality rate in the 1979 accidental aerosol release of anthrax at Sverdlovsk is estimated to be about 70%, while in the 2001 U.S. anthrax letters cases, 5 of 11 individuals with inhalation anthrax died, for a mortality rate of 45%. Many of the patients in the latter series of cases received intensive medical care, which likely contributed to a lower mortality rate than that seen in Sverdlovsk.

> to every person on that day; only those who have been declared WIA are modeled to begin receiving antibiotics on that day. Those who are declared WIA after $d_{trt\text{-}anth}$ are modeled to begin receiving antibiotics on the day they are declared WIA.

Although this is stated as a limitation, it is actually the most sensible way to apply treatment.

Human Response Model (*AMedP-7.5 Tables 5-6 to 5-8*)

Infectivity

A common estimate for the ID_{50} of *B. anthracis* is 8,000–10,000 spores. An unclassified 1997 report (the JAYCOR report) summarizing the tests conducted for the anthrax program between 1953 and 1964[539] provides unclassified evidence regarding the sources of the estimate of 8,000 spores: a 1961 laboratory test involving 34 NHPs, which generated an estimate of 8,689 spores, and a subsequent 1962 summary, which stated the result as 8,000 spores. Following the citation trail from recent publications leads to a 1986 Defense Intelligence Agency (DIA) publication[540] that reports an LD_{50} of 8,000—10,000 spores, without attribution. No citation trail exists linking the DIA publication to the publications from the 1960s, but these findings are suggestive. Given the small number of NHPs used in the tests and, more important, the fact that the NHP minute volumes were *assumed*, not measured, we believe that the data from the 1961 laboratory test are of low quality relative to other available NHP data. We believe that the 1961 data are indeed the source of the estimate—although it cannot be proven from the literature—and thus find the fact that "the 8,000 LD50 has never been approved as the human LD50 by the Chemical Corps for lack of validation"[541] to be in support of the idea that the 1961 data are of low quality and should not be used as the basis for a model to be applied to humans.

In developing *AMedP-8*(*C*), the authors of that document noted some of the problems with the 8,000–10,000 spore estimate and, after a literature survey, used data from a paper by Druett et al.[542] to derive an ID_{50} estimate of 41,000 spores.[543] However, a recent IDA

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539 M. Thomas Collins and Clyde R. Replogle, *An Analysis of the Respiratory Infectivity of Bacillus anthracis*, AL/CF-TR-1997-0078 (Beavercreek, OH: JAYCOR, June 1997), CRITICAL TECHNOLOGY.

540 Defense Intelligence Agency (DIA), *Soviet Biological Warfare Threat*, DST-161OF-057-86 (Washington, DC: Defense Intelligence Agency, 1986), https://www2.gwu.edu/~nsarchiv/NSAEBB/NSAEBB61/Sverd26.pdf.

541 Collins and Replogle, *Respiratory Infectivity of Bacillus anthracis,* 9.

542 H. A. Druett et al., "Studies on Respiratory Infection. I. The Influence of Particle Size on Respiratory Infection with Anthrax Spores," *Journal of Hygiene* 51, no. 3 (1953): 359–371.

543 NATO, *AMedP-8*(*C*), A-35 and C-79.

analysis[544] has determined that many older (pre-1990) experiments, including those reported by Druett et al. and those we believe are the source of the 8,000–10,000 spore estimate, used laboratory methods that call into question the validity of the data in comparison to modern techniques. Specifically, the issues are assumed (rather than measured) individual NHP minute volumes and lack of confirmation of an appropriate mass median aerodynamic diameter (MMAD) (<5 µm).

The recent IDA analysis mentioned above included a wide-sweeping literature survey that identified over 30 sources reporting on NHP inhalation experiments. Of those 30, only 11 measured minute volumes for individual NHPs, confirmed appropriate MMAD, presented data for NHPs not vaccinated or given some other form of medical treatment, and reported dose in an unambiguous way. The 11 sources provided data on 171 NHPs (97 rhesus macaques (RMs), 34 CMs, and 40 African green monkeys (AGMs)). The 171 data points were selected from the larger set of available data with the purpose of identifying a high-quality dataset that could be used to develop a new infectivity model. Unfortunately, a large portion of the data are labeled FOUO within the United States; if FOUO information is included in a NATO document, that document must be marked NATO UNCLASSIFIED, a marking we were directed to avoid for *AMedP-7.5*. Although we have requested that the FOUO data be downgraded so that the updated estimate can be included in *AMedP-7.5*, a determination had not yet been made at the time *AMedP-7.5* and this TRM were required to be completed.

Therefore, *AMedP-7.5* includes an arbitrarily chosen ID_{50} that is between the historical estimate of 8,000–10,000 spores and the *AMedP-8*(*C*) value of 41,000 spores, reasonably representative of the value derived in the IDA analysis that cannot yet be included in NATO documents, and rounded to a single significant digit to avoid implying false precision: 20,000 spores. Because it is a generic value often used for infectious agents, *AMedP-7.5* also includes a corresponding probit slope of 1 probit/log (dose).

Ideally, the FOUO data will be downgraded soon, and the infectivity model derived in the not-yet-published IDA analysis will be included in the next version of *AMedP-7.5*.

Lethality

MABW states that "mortality has been essentially 100% in the absence of appropriate treatment."[545] After reviewing identified cases of inhalational anthrax occurring between 1900 and 2005, Holty et al. concluded that the CFR is 100% even if treatment is applied,

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544 Publishing has been delayed as we await potential downgrading of certain data that are currently FOR OFFICIAL USE ONLY. The paper, once published, will be: Sean M. Oxford, Julia K. Burr, and Carl A. Curling, *Infectivity Models for Bacillus anthracis Volume I: Main Body*, IDA Paper P-5254 (Alexandria: VA, IDA).

545 Purcell, Worsham, and Friedlander, "Anthrax," 76.

when said treatment does not start before the onset of the fulminant stage of disease[546] (equivalent to Stage 2 in the *AMedP-7.5* model—see Subsection 0. In reviewing various other literature sources for data for the other submodels, we found that a 100% CFR was often repeated. *AMedP-7.5* uses a 100% CFR for untreated inhalational anthrax.

Incubation Period

There have been a few human inhalation anthrax cases in the last century. For these, only a limited amount of data exist regarding incubation. Because many of these cases followed inhalation exposure during wool or other animal hair processing, there is a lack of exact information about when exposure occurred. The largest U.S. outbreak occurred during the Amerithrax events of 2001; the exact period of exposure for most of those exposed, however, is unknown and therefore not useful for determining the duration of incubation.

The most notable exception to the general dearth of useful case data is the inhalation anthrax outbreak, which occurred in Sverdlosk, Russia, in 1979.[547] Note that even these data have been questioned; the source of the outbreak remains unclear—initially an ingestion-based outbreak was reported due to contaminated meat, but more recent statements indicate an unintentional release from a local factory.[548] In addition, the exact case reporting—including numbers of ill, population distribution, etc.—has been questioned. However, the few incubation period models that have been published utilize or have been compared to the data available from the Sverdlosk outbreak. Some models for the length of incubation period have tried to take into account the physiological processes, including the competing aspects of clearance and germination to describe the risk and likely durations associated with a dose-based anthrax exposure.[549] Others employ simpler lognormal distributions or parametric, dose-based lognormal distributions of the incubation period.[550]

In 2006, Wilkening reviewed four different inhalation models utilizing the Sverdlosk data. Three of the reviewed models posited infectivity as a function of dose modeled as cumulative lognormal distributions with varying median infective doses and probit slopes.

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546 Jon-Erik C. Holty et al., "Systematic Review: A Century of Inhalational Anthrax Cases from 1990 to 2005," *Annals of Internal Medicine* 144, no. 4 (2006): 272–274.

547 Ron Brookmeyer, Elizabeth Johnson, and Sarah Barry, "Modeling the Incubation Period of Anthrax," *Statistics in Medicine* 24, no. 4 (February 2005): 531–542.

548 Matthew Meselson et al., "The Sverdlovsk Anthrax Outbreak of 1979," *Science* 266, no. 5188 (November 1994): 1202–1208; and Dean A. Wilkening, "Sverdlosk Revisited: Modeling Human Inhalation Anthrax, Supporting Text." *Proceedings of the National Academy of Sciences of the Unites States of America* 103, no. 20 (2006): supplement.

549 Brookmeyer, Johnson, and Barry, "Incubation Period of Anthrax."

550 Ibid.; and Wilkening, "Sverdlosk Revisted," 7589–7594.

The fourth model used an exponential distribution based on the competing physiological aspects of the disease—clearance and germination.[551]

The incubation period of anthrax has been assessed to be as short as 1 to 5 days[552] and as long as 2 to 60 days.[553] The Sverdlosk data suggested a modal incubation period of 9 to 10 days, with the longest incubation period being 43 days.[554] Wilkening concluded that this information suggested dose dependence of the incubation period. He then assumed a lognormal distribution, based on previous work by Sartwell.[555] The result is a parametric, dose-based lognormal distribution, with parameters derived from Glassman.[556] The CDF for the parametric lognormal distribution given in the "Supporting Text" of Wilkening's article is given in Equation 18.[557]

$$\mathrm{F}_{inc-anth}(t) = \left(\frac{1}{\sigma\sqrt{2\pi}}\right)\int_0^t \left(\frac{1}{x}\right) e^{-\frac{(\ln(x)-\ln(\mu))^2}{2\sigma^2}}\, dx \qquad (18)$$

where:

$\mathrm{F}_{inc-anth}(t)$ is the cumulative fraction of persons with anthrax who have completed the incubation period and entered Stage 1 of the disease by the end of Day *t*,

$\mu = 10.3 - 1.35\times\log_{10}(\text{dose})$, and

$\sigma = 0.804 - 0.079\times\log_{10}(\text{dose})$.

Wilkening did not prescribe upper and lower dose thresholds for which the equation applied. We applied it to doses as low as 10^2 spores and as high as 2×10^7 spores to create dose ranges, each having an associated incubation period distribution. The lowest dose range is for $<10^2$ spores because the probability of infection at 10^2 spores is only 1.1%, and there seemed no good reason create yet another dose range for lower doses covering such a small fraction of the ill population. The highest dose range is $>10^7$ spores because once the dose increases past $\sim2\times10^7$ spores, the entire population completes incubation within 1

551 Wilkening, "Sverdlosk Revisted," 7589–94.

552 David R. Franz et al., "Clinical Recognition and Management of Patients Exposed to Biological Warfare Agents," *Journal of the American Medical Association* 278, No. 5 (1997), 400–401; and Purcell, Worsham, and Friedlander, "Anthrax," 74.

553 Virginia Department of Health, "Anthrax: Guidance for Health Care Providers" (2004) http://www.vdh.state.va.us/EPR/pdf/AnthraxGuidance12092004.pdf.

554 Meselson et al., "Sverdlovsk Anthrax Outbreak," 1207.

555 Sartwell, P. (1950) *American. Journal of Hygiene*, 51, 310–318, as referenced by Wilkening.

556 Harold N. Glassman, "Industrial Inhalational Anthrax: Discussion," *Bacteriological Review* 30 (1966): 658.

557 Wilkening, "Sverdlosk Revisited," supplement.

day, so there would be no relevant change at higher doses because the *AMedP-7.5* time resolution for reporting is 1 day. A dose of 2×10^7 spores was used to calculate the incubation period parameters for the highest dose range, and the highest dose in each other dose range was used to calculate each respective incubation period distribution. Table 149 summarizes the results of the process described above. The first, second, and fourth columns are also presented as a table-within-a-table in *AMedP-7.5* Table 5-8.

Table 149. Anthrax Incubation Period by Dose Range in *AMedP-7.5*

Dose Range Label	Mean (days)	μ	Standard Deviation (days)	σ
A	9.36	2.028	6.74	0.646
B	7.34	1.833	4.52	0.567
C	5.52	1.589	2.86	0.488
D	3.86	1.267	1.65	0.409
E	2.32	0.788	0.79	0.330
F	0.88	–0.163	0.22	0.251
G	0.46	–0.813	0.10	0.227

The higher dose ranges fall more within the previously cited 1–5 day incubation period, and the lower dose ranges fall more within the previously cited 2–60 day incubation period. Although this TRM will not normally show visuals of the distributions, the complicated nature of the anthrax incubation period makes it helpful here—see Figure 13.

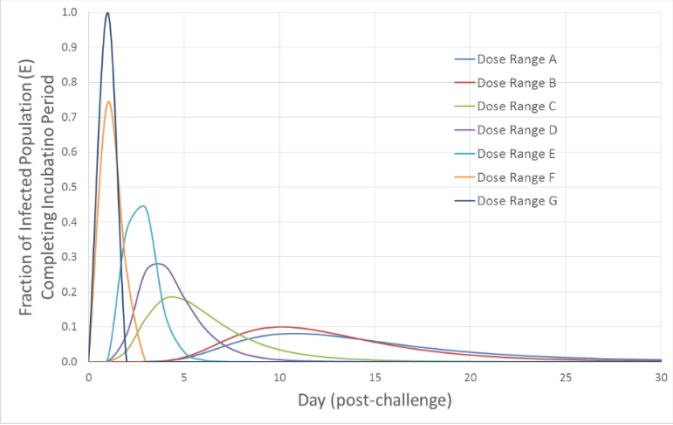

Figure 13. Visualization of Anthrax Incubation Period Distribution by Dose Range

Injury Profile

Anthrax is commonly modeled as a biphasic, or two-stage, disease, with the two stages described as prodromal, or initial, and fulminant. Using descriptions from

Brachman,[558] Jernigan et al.,[559] Inglesby et al.,[560] and Holty et al.,[561] each stage of anthrax was associated with signs and symptoms and their associated severity as shown in Table 150. Depending on the dose and physiological manifestation of the disease, there may be a brief mitigation or even cessation of symptoms between these two periods (hours) that is not captured by the Injury Profile.

Table 150. Untreated Anthrax Injury Profile

	Stage 1	Stage 2
Signs and Symptoms (S/S)	Flu-like symptoms including malaise, fatigue, drenching sweats, fever, headache, and chills; nausea and vomiting; nonproductive cough; mild chest discomfort and dyspnea; myalgia	Persistent fever; sudden onset of increasing respiratory distress (increased chest pain, dyspnea, stridor, cyanosis, and diaphoresis) leading to respiratory failure and eventual death; tachycardia, tachypnea, hypotension, leading to cardiovascular collapse and death; altered neurological status (confusion, syncope, or coma) meningoencephalitis likely; edema of chest and neck may be present; pleural effusion and likely widening and edemas of the mediastinum
S/S Severity	2 (Moderate)	4 (Very Severe)

Duration of Illness

The work of Holty et al. was chosen for use in modeling the duration of illness in *AMedP-7.5* because its descriptions of the two stages of illness are consistent with those in the *AMedP-7.5* Injury Profile and because it provided specific quantitative estimates of the time spent in each stage based on a review of 2,500 journal articles.

During their review of human anthrax cases from 1900 to 2005, Holty et al. extracted disease progression information for 82 patients, some of whom had received antibiotic treatment. For those patients who received no antibiotics, the mean durations of illness were 3.8 days and 0.8 days for the prodromal and fulminant stages, respectively. However, the study authors felt that these data were skewed because patients with short prodromal stages were more likely to progress to the fulminant stage of illness without seeking medical treatment.

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558 Philip S. Brachman, "Inhalational Anthrax," *Annals of the New York Academies of Science* 353 (December 1980): 85–92.

559 John A. Jernigan et al., "Bioterrorism-Related Inhalational Anthrax: The First 10 Cases Reported in the United States," *Emerging Infectious Diseases* 7, no. 6 (November–December 2001): 933–944.

560 Thomas V. Inglesby et al., "Anthrax as a Biological Weapon, 2002: Updated Recommendations for Management," *Journal of the American Medical Association* 287, no. 17 (May 2002): 2238–2244.

561 Holty et al., "Systematic Review," 272–275.

To account for this bias, Holty et al. conducted maximum likelihood analyses using all cases for which time estimates were available, with cases considered to be right-censored if the progression of disease was halted by antibiotic intervention. The resulting lognormal maximum likelihood estimates for the mean time in the prodromal and fulminant stages are 4.2 (with standard deviation = 2.3) and 0.7 (with standard deviation = 0.74) days, respectively. The associated lognormal distribution parameters are μ = 1.304 and σ = 0.512 for Stage 1, and μ = –0.732 and σ = 0.866 for Stage 2.

Medical Countermeasures and Treatment Model

Medical management of inhalation anthrax has two primary objectives: preventing onset of the disease through vaccination or chemoprophylaxis and, if that fails, administering antibiotics as quickly as possible after the onset of symptoms. Supportive care typically focuses on reducing toxin load in the body and assisting respiration as needed.

Pre-Exposure and Post-Exposure Prophylaxis

Anthrax Vaccine Adsorbed (AVA), also known as BioThrax, is U.S. Food and Drug Administration (FDA)-approved for pre-exposure prophylaxis as a series of five shots over 18 months, with annual boosters. It may also be used off-label as post-exposure prophylaxis (three shots over 4 weeks) in combination with a 60-day course of antibiotics.[562] Below we discuss the efficacy of three different prophylaxis options: pre-exposure vaccination, pre-exposure vaccination plus post-exposure antibiotics, and post-exposure vaccination and antibiotics.

The human efficacy study by Brachman et al. tested the efficacy of a precursor to BioThrax on workers at four goat hair processing mills. Based on their results, the authors estimated the efficacy to be 0.925;[563] however, none of the workers were directly challenged with a known dose of *B. anthracis*.

To estimate the vaccine efficacy based on known exposures, we consulted several studies conducted on RMs, which are considered to be the most appropriate model for human inhalation anthrax.[564] As shown in Table 151, we identified 5 studies providing data on pre-exposure vaccination efficacy tests with 66 RMs, 63 of which survived, for an overall efficacy of 95.5%. Looking at strain-specific results, one could conclude that AVA

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562 Centers for Disease Control and Prevention (CDC), “Anthrax Prevention,” last updated January 14, 2016, http://www.cdc.gov/anthrax/medical-care/prevention.html.

563 Philip S. Brachman et al., “Field Evaluation of a Human Anthrax Vaccine,” *American Journal of Public Health* 52, no. 4 (April 1962): 644.

564 M. L. M. Pitt et al., “Comparison of the Efficacy of Purified Protective Antigen and MDPH to Protect Non-Human Primates from Inhalation Anthrax,” Special Supplement, *Salisbury Medical Bulletin* 87 (1996): 130.

is 97.8% efficacious against the Ames strain but only 90% efficacious against the ASIL K9729/Turkey strain. To account for this uncertainty and to provide a conservative estimate, *AMedP-7.5* uses a pre-exposure vaccination efficacy of 90%.

Table 151. Pre-Exposure Anthrax Vaccination Efficacy Data in Rhesus Monkeys

Source	Vaccine	*B. anthracis* Strain	Total # RMs	# RMs Protected	Efficacy
Pitt et al, 1996	MDPH	Ames	10	10	1
Ivins et al., 1996	MDPH (8 weeks pre-challenge)	Ames	10	10	1
———	MDPH (38 weeks pre-challenge)	Ames	3	3	1
———	MDPH (100 weeks pre-challenge)	Ames	8	7	0.875
Ivins et al., 1998	AVA	Ames	10	10	1
Fellows et al., 2001	AVA	ASIL K9729/Turkey	10	10	1
———	AVA	ASIL K9729/Turkey	10	8	0.8
Livingston et al., 2010	BioThrax	Ames	5	5	1

Note: See Appendix B for full reference citations.

Note: Although we report the vaccine as either MDPH, AVA, or BioThrax based on how it is stated in the source, they are all the same vaccine.

In a study of the efficacy of post-exposure prophylaxis against inhalational anthrax in RMs, Friedlander et al. found that a combination of vaccination and antibiotic therapy was completely effective in preventing the onset of the disease. Eight of 10 RMs treated with vaccine alone died; clinical presentation and time to death did not differ from that observed in control animals. Three groups of 10 animals each were treated with antibiotics alone for 30 days: 1 with penicillin, 1 with doxycycline, and 1 with ciprofloxacin. One animal in the ciprofloxacin group died during the period of therapy for reasons determined to be unrelated to the experiment and was eliminated from consideration; all other animals survived the period of therapy, and none developed symptoms of disease during this time. However, some animals developed anthrax and died after the period of therapy ended, including three in the penicillin group and one each in the doxycycline and ciprofloxacin groups. A fifth group of 10 animals was both vaccinated and given doxycycline. One of these animals died during the period of study from undetermined causes and was eliminated from further consideration; all others survived both an initial inhaled challenge dose of 4.0

± 1.6×10^5 spores and a re-challenge 131 to 142 days later with 2.6 ± 1.6×10^6 spores, and all remained disease-free at the time of study publication.[565]

The Friedlander et al study demonstrated that antibiotic therapy staves off infection long enough to allow a vaccine-generated immune response to develop. Vietri et al.[566] later confirmed that post-exposure vaccination plus antibiotics are completely effective, showing that 10 RMs that were vaccinated and given ciprofloxacin survived challenges of approximately 1,600 LD_{50} of aerosolized anthrax spores. Kao et al. confirmed that post-exposure antibiotics alone are effective while antibiotic treatment is ongoing but that in the absence of immune response, germination of residual spores could result in death after antibiotic treatment ends.[567] These studies and their findings are the basis of CDC recommendations that post-exposure vaccination and antibiotics should be used together.

Based on CDC recommendations and the evidence cited above, *AMedP-7.5* does not include an option for post-exposure vaccination alone or post-exposure antibiotics alone—we do not believe any medical system would respond so inappropriately. *AMedP-7.5* includes two post-exposure prophylaxis options: either adding post-exposure antibiotics to pre-exposure vaccination or administering both vaccination and antibiotics post-exposure. Based on the data discussed above, both options are modeled with 100% efficacy.

Lethality

The lethality model for those who have become ill and are receiving treatment including antibiotics is based on U.S. experience with the Amerithrax patients (admittedly a small dataset), as presented by Holty et al. Specifically, Holty et al. assigned a CFR of 100% to patients who do not begin receiving antibiotic treatment before the onset of the fulminant state (Stage 2 in *AMedP-7.5*). For patients who begin receiving antibiotic treatment while in Stage 1, Holty et al. assigned a CFR calculated according to Equation 19, in which the parameter d is time between disease onset and antibiotic treatment, measured in days.[568]

$$CFR(d) = 1.2\left(\frac{\%}{\text{day}}\right) \times d\ (\text{days}) + 10(\%) \tag{19}$$

565 Arthur M. Friedlander et al., "Postexposure Prophylaxis against Experimental Inhalation Anthrax," *Journal of Infectious Diseases* 167, no. 5 (1993), 1239–1243.

566 Nicholas J. Vietri et al., "Short-Course Postexposure Antibiotic Prophylaxis Combined with Vaccination Protectst against Experimental Inhalational Anthrax," *Proceedings of the National Academy of Sciences* 103, no. 20 (2006), 7813–7816.

567 L. Mark Kao et al., "Pharmacokinetic Considerations and Efficacy of Levofloxacin in an Inhalational Anthrax (Postexposure) Rhesus Monkey Model," *Antimicrobial Agents and Chemotherapy* 50, no. 11 (November 2006): 3535–3542.

568 Holty et al., "Systematic Review," 272.

Injury Profile

The Injury Profile discussed in Subsection 0 is for untreated patients. The review of inhalational anthrax cases by Holty et al.[569] and the case histories of the 2001 anthrax letters cases published by Jernigan et al.[570] suggest that while the duration of illness varies for survivors and non-survivors, treated or untreated, the basic presentation of illness remains generally the same. Thus, the two stages of illness described in Table 150 are still applied to all patients. At the end of Stage 2, non-survivors die and survivors progress to Stages 3 (gradual recovery in the hospital) and then Stage 4 (recovery that occurs during an extended convalescent period at home). This information is summarized in Table 154.

Duration of Illness

The Holty et al. review identified 36 cases from 1900 to 2005 where inhalational anthrax was treated with either antibiotics, anthrax antiserum, or both. Overall, these treatments prolonged both the prodromal and fulminant stages of disease beyond what was typically observed in untreated cases. Holty et al. used a maximum likelihood estimator to derive both Weibull and lognormal distributions of duration of both the prodromal and fulminant stages of disease.[571] We chose to use their lognormal distribution for consistency with the untreated anthrax duration of illness model.

In cases where antibiotic treatment was initiated in the prodromal phase, Holty et al., estimated the mean duration of prodromal and fulminant stages of anthrax to be 5.8 (standard deviation = 2.0) and 1.4 (standard deviation = 1.8) days, respectively, corresponding to $\mu = 1.702$ and $\sigma = 0.335$ (Stage 1) and $\mu = -0.151$ $\sigma = 0.988$ (Stage 2). Where antibiotic treatment was delayed until the fulminant stage of illness (Stage 2), that stage was still prolonged: the mean duration of the fulminant stage was 1.5 days (standard deviation = 1.3),[572] corresponding to $\mu = 0.125$ and $\sigma = 0.749$.

The Holty et al. review did not characterize the time between the end of the fulminant stage of the disease and recovery for survivors, all of whom would have initiated antibiotic treatment during the prodromal phase of illness. However, the case histories from 10 of the 11 inhalation anthrax cases from the Amerithrax event are instructive. As shown in Table 152, the average duration of the initial phase was 4 days for survivors and 5 days for non-survivors; to some extent this difference can be attributed to delays in hospitalization for two of the non-survivors (Cases 5 and 6), who were initially misdiagnosed. Regardless, the data are not inconsistent with the untreated Stage 1 duration of illness model.

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569 Ibid., 270–280.

570 Jernigan et al., “Bioterrorism-Related Inhalational Anthrax.”

571 Holty et al., “Systematic Review,” W-44–W-45.

572 Ibid., Appendix Table 4: W-52.

Table 152. Duration of Illness for 10 U.S. Inhalational Anthrax Cases

Case	Outcome	Time from Onset to Hospitalization (days)	Time from Hospitalization to Death or Discharge (days)
1	Death	5	3
2	Recovery	7	22
3	Recovery	3	24+
4	Recovery	4	20
5	Death	5	<1
6	Death	6	1
7	Recovery	2	16
8	Recovery	5	17
9	Recovery	3	8
10	Death	3	4
Average (survivors)		**4**	**18**
Average (non-survivors)		**5**	**2**

All six survivors of the 2001 anthrax letters cases were near the end of the first phase of illness when they first sought medical care. All six were promptly hospitalized and administered appropriate antibiotics on that same day. All four non-survivors were in the second stage of illness when they were hospitalized and appropriate antibiotics were administered.[573]

All non-survivors, despite being treated aggressively in an ICU setting, died, on average, 2 days after admission to the hospital (consistent with 1.5-day mean and 1.3-day standard deviation lognormal distribution from Holty et al.). Survivors, on average, remained hospitalized in an ICU setting for approximately 18 days; upon release they typically continued oral antibiotic therapy for several weeks.[574]

Although the Holty et al. review did not characterize the time between the end of the fulminant stage of the disease and recovery for survivors, all of whom would have initiated antibiotic treatment during the prodromal phase of illness, Table 152 shows that the Amerithrax survivors spent an average of 18 days in the hospital. Subtracting the combined mean duration of Stage 1 and Stage 2 when antibiotics are started in Stage 1—7.2 days—gives an estimate of 11 days for Stage 3.

Finally, individuals who survive inhalational anthrax require an extensive period of convalescence, during which they continue to receive antibiotic treatment to counter

573 Jernigan et al., “Bioterrorism-Related Inhalational Anthrax,” 940.

574 Jernigan et al., “Bioterrorism-Related Inhalational Anthrax.”

delayed germination of anthrax spores. Although at present limited data exist regarding the overall extent and nature of the convalescent period, long-term consequences of the disease, and CDC recommendation of 60 days of antibiotics, we assumed patients could not RTD until 60 days after being released from the hospital.

Although this is only anecdotal, a case of naturally occurring inhalational anthrax in Minnesota involved a 61-year old man whose case history closely mirrored that observed in the 2001 survivor cases.[575] The man had been suffering fatigue at the end of a lengthy vacation and became seriously ill while visiting friends in Minnesota in early August 2011. He was hospitalized with a preliminary diagnosis of pneumonia on August 4 and subsequently diagnosed with inhalational anthrax the next day, after which he was treated with intravenous ciprofloxacin and clindamycin. The man was also treated with anthrax immune globulin derived from the serum of vaccinated individuals. The man was released after 25 days of hospitalization (in his case, representing the end of Stage 1 through the end of Stage 3), most of it in intensive care, with instructions to continue taking oral ciprofloxacin for 60 days per CDC recommendations.

Model Summary

Table 153 and Table 154 summarize the model parameters for anthrax used in *AMedP-7.5*. While the parameters in these tables represent current best estimates, any new data that become available could be incorporated and may improve the model, particularly for the infectivity model, since the other models are based on human data, and for the treated duration of illness model, since it is based on a small number of data points.

Table 153. Anthrax Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 20,000 spores Probit slope = 1 probit/log (dose)
• Pre-exposure vaccination	Rate (efficacy)	90%
• Pre-exposure vaccination plus post-exposure antibiotics	Rate (efficacy)	100%
• Post-exposure vaccination plus antibiotics	Rate (efficacy)	100%

575 Robert Roos, "Early Diagnosis and Treatment Helped Florida Man Beat Anthrax," *Center For Infectious Disease Research and Policy* (*CIDRAP*) *News*(30 August 2011), http://www.cidrap.umn.edu/cidrap/content/bt/anthrax/news/aug3011anthrax.html; ProMED-mail, "Anthrax—USA (09): (Minnesota)," (International Society for Infectious Diseases, 31 August 2011).

Lethality		
• Untreated or Treatment Initiated in Stage 2	Rate	100%
• Treatment Initiated in Stage 1	Linear function	m = 1.2 %/day b = 10%
Incubation period	Dose-Dependent Lognormal Distribution	See Table 149
Duration of illness		
• Stage 1 (untreated)	Lognormal distribution	Mean = 4.2 days Standard deviation = 2.3 days μ = 1.304; σ = 0.512
• Stage 2 (untreated)	Lognormal distribution	Mean = 0.70 days Standard deviation = 0.74 days μ = -0.732; σ = 0.866
• Stage 1 (treatment initiated in Stage 1)	Lognormal distribution	Mean = 5.8 days Standard deviation = 2.0 days μ = 1.702; σ = 0.335
• Stage 2 (treatment initiated in Stage 1)	Lognormal distribution	Mean = 1.4 days Standard deviation = 1.8 days μ = -0.151; σ = 0.988
• Stage 2 (treatment initiated in Stage 2)	Lognormal distribution	Mean = 1.5 days Standard deviation = 1.3 days μ = 0.125; σ = 0.749
• Stage 3 (survivors)	Constant	11 days
• Stage 4 (survivors)	Constant	60 days

Table 154. Anthrax Injury Profile

	Stage 1	Stage 2	Stage 3 (survivors)	Stage 4 (survivors)
Signs and Symptoms (S/S)	Flu-like symptoms including malaise, fatigue, drenching sweats, fever, headache, and chills; nausea and vomiting; nonproductive cough; mild chest discomfort and dyspnea; myalgia	Persistent fever; sudden onset of increasing respiratory distress (increased chest pain, dyspnea, stridor, cyanosis, and diaphoresis) leading to respiratory failure; tachycardia, tachypnea, hypotension, leading to cardiovascular collapse and death; altered neurological status (confusion, syncope, or coma) meningoencephalitis likely; edema of chest and neck may be present; pleural effusion and likely widening and edemas of the mediastinum	Resolution of fever, gradual cessation of acute symptoms	Malaise, weakness
S/S Severity	2 (Moderate)	4 (Very Severe)	3 (Severe)	CONV

Cohorts and Special Considerations (*AMedP-7.5 Section 5.2.1.3*)

The definitions of the cohorts are sufficiently explained in *AMedP-7.5*. This section explains the equations used to calculate the cohort populations; for definitions of the variables in the equations, see *AMedP-7.5*.

Equation 5-35: In each dose range, those who have already died before $d_{trt\text{-}anth}$

Equation 5-36: In each dose range, those who have already entered Stage 2 before $d_{trt\text{-}anth}$, minus those who have already died.

Equation 5-37:

$$F_{DR,T-1} = E_{DR} \cdot \left[\sum_{d_{Stg1}=1}^{d_{trt\text{-}anth}} \left(p_{f,T-1} \cdot PDT_{5\text{-}9}(d_{Stg1}) \cdot P_{in\text{-}Stg1} \right) + 0.1 \cdot \left(1 - \sum_{d=1}^{d_{trt\text{-}anth}} PDT_{5\text{-}9}(d) \right) \right]$$

Total # of ill in dose range

CFR for fraction of E_{DR} that entered Stg1 on a given day

Fraction of E_{DR} that entered Stg1 on a given day

Probability that those who entered Stg1 on the given day are still in Stg1

Sum over different days on which individuals could have entered Stg1

CFR if receiving antibiotics as soon as symptoms begin

Fraction of E_{DR} still incubating

Equation 5-38: In each dose range, those who became sick minus those who are assigned to one of the F cohorts

Equation 5-39: An implementation of the treatment initiated in Stage 1 lethality model

Equation 5-40: In each dose range, those who have already died before $d_{trt\text{-}anth}$

Equation 5-41: The remainder of the ill, after subtracting those who have already died before $d_{trt\text{-}anth}$

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1.20. Brucellosis Model
(*AMedP-7.5 Section 5.2.2*)

Introduction

Brucellosis, also known as undulant fever, is caused by a gram-negative bacterium of the genus *Brucella*. Four major *Brucella* species produce brucellosis in humans: *B. melitensis*, prevalent among goats and sheep; *B. abortus*, predominantly found in cattle; *B. suis*, common in pigs; and *B. canis*, naturally found in dogs.[576] The majority of human cases worldwide are caused by *B. melitensis*, although *B. abortus* infection is also somewhat common and occurs over a much larger geographical area, including the United States.[577]

Brucellosis is a zoonotic disease, and contraction by humans is generally the result of close contact with infected animals or their byproducts; consumption of unpasteurized, contaminated milk; or improper laboratory procedure. In fact, the combined general lack of awareness of *Brucella* as a potential biohazard and high risk of aerosol transmission have made brucellosis one of the most commonly acquired laboratory diseases.[578] Although human-to-human transmission has been implicated in at least one case of brucellosis,[579] the spread of disease through such means is generally considered to be very rare.[580] For the purposes of *AMedP-7.5*, brucellosis was treated as a noncontagious disease, and no attempt was made to quantify the rate of its secondary person-to-person spread.

Assumptions, Limitation, and Constraint (*AMedP-7.5 Section 5.2.2.2*)

> **Assumption**: The presentation and duration of brucellosis symptoms are independent of the route of exposure.

This is found to be well-supported by the literature,[581] but not necessarily proven, hence its statement as an assumption.

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576 J. Staszkiewicz et al., "Outbreak of *Brucella melitensis* Among Microbiology Laboratory Workers in a Community Hospital," *Journal of Clinical Microbiology* 29, no. 2 (February 1991): 287.

577 Jorge C. Wallach et al., "Human Infection by *Brucella melitensis*: An Outbreak Attributed to Contact with Infected Goats," *FEMS Immunology and Medical Microbiology* 19 (1998): 315.

578 E. Gruner et al., "Brucellosis: An Occupational Hazard for Medical Laboratory Personnel: Report of Five Cases," *Infection* 22, no. 1 (1994): 34.

579 Bruce Ruben et al., "Person-to-Person Transmission of *Brucella melitensis*," *The Lancet* 337 (January 1991): 14–15.

580 Bret K. Purcell, David L. Hoover, and Arthur M. Friedlander, "Brucellosis," chap. 9 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), 187.

581 Purcell, Hoover, and Friedlander, "Brucellosis," 189.

Assumption: Half of all cases are "abrupt," and the other half are "insidious."

This is also found to be well-supported by the literature,[582] but not necessarily proven, hence its statement as an assumption.

Assumption: One organism, one cell, and one CFU are equivalent.

This assumption was necessary because the sources from which the models were derived tended to use the terms "organism," "cell," and "CFU" as if they were interchangeable.

Assumption: Those who receive treatment will have a 4-week CONV period after their symptoms end (this period is reflected in the PDTs), before RTD.

This assumption reflects reality in the sense that convalescence is often necessary, but the specific timeline of 4 weeks is arbitrary based on professional judgment.

Limitation: Although the model requires the user to specify a day on which antibiotic treatment becomes available ($d_{trt\text{-}bruc}$), it does *not* apply treatment to every person on that day; only those who have been declared WIA are modeled to begin receiving antibiotics on that day. Those who are declared WIA after $d_{trt\text{-}bruc}$ are modeled to begin receiving antibiotics on the day they are declared WIA.

Although this is stated as a limitation, it is actually the most sensible way to apply treatment.

Constraint: The models apply to *B. abortus*, *B. melitensis*, and *B. suis*.

This constraint is based on the data from which the models were developed and the finding during model development that there seemed to be no difference between the disease produced by the different strains.

Human Response Model (*AMedP-7.5 Tables 5-17 and 5-18*)

B. melitensis is more likely to lead to severe complications than the other species,[583] although case reports describe the same general illness from all species. The metric of interest for most submodels appeared to be independent of the species, so case data from patients infected with different species were combined. The infectivity submodel was

582 Ibid.

583 F. Jacobs et al., "Brucella Endocarditis: The Role of Combined Medical and Surgical Treatment," *Reviews of Infectious Diseases* 12, no. 5 (September – October 1990): 741.

derived entirely from *B. melitensis* cases only because cases from other species were excluded based on other criteria.

Infectivity

Although experimental studies on the infectivity of *Brucella* in humans occurred as early as the late 1920s,[584] nearly a century later, a generally accepted human model of infectivity as a function of the inhaled dose of organisms has yet to be developed. Those early human experiments, conducted by Morales-Otero in Puerto Rico on 40 volunteers, compared the ability of 14 different strains of *B. abortus* to infect people through various routes, including ingestion and dermal exposure (to normal and abraded skin). Notably, a dose-response relationship was not recorded, nor was inhalation evaluated as a route of exposure. Since then, naturally occurring and accidental laboratory outbreaks in humans have been documented, yet no dose-dependent human inhalation infectivity data have been recorded.

MABW states only that brucellae are highly infectious in laboratory settings and by the airborne route, but provides no quantitative estimates for the infectivity in humans (or animals).[585] In contrast, the *P-8 BMR* presents an infectivity model derived from inputs for brucellosis provided by SMEs: a median infective dose (ID_{50}) of 14.1 organisms and a probit slope of 8.52 probits/$\log_{10}$ dose. The SMEs reportedly provided the following estimates for infectivity: an ID_{10} of 10 organisms, an ID_{50} of 12 organisms, and an ID_{90} of 20 organisms. Because the three values were inconsistent with a lognormal distribution of infectivity response, however, the authors of the *P-8 BMR* derived their values solely from the 10% and 90% KAMI infectivity estimates, assuming a lognormal distribution.[586]

The SME-estimated median infective dose of 12 organisms is referenced to a "swine model" from a Russian journal article[587] and is applicable to particles from 0.3 to 1.5 microns. The cited article actually references these values to a guinea pig study by Druett et al. in 1956.[588] The ID_{10} and ID_{90} values are more difficult to trace to original data; the annex in the *P-8 BMR* provides only a vague statement regarding their origin.

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584 P. Morales-Otero, "Further Attempts at Experimental Infection of Man with a Bovine Strain of *Brucella abortus*," *The Journal of Infectious Diseases* 52, no. 1 (January–February 1933): 54–59.

585 Purcell, Hoover, and Friedlander, "Brucellosis," 187 and 192.

586 Anno et al., *AMedP-8* (*Biological*) *Methods Report*, 206.

587 K. G. Gapochko and V. I. Ogarkov, "Effect of the Primary Distribution of the Microbial Aerosol in the Respiratory System on the Size of the Infecting Dose (A Review of the Literature)," *Zh Mikrobiol Epidemiol Immunobiol* 50, no. 9 (September 1973): 3–6.

588 H. A. Druett, D. W. Henderson, and S. Peacock, "Studies on Respiratory Infection. III. Experiments with *Brucella suis*," *The Journal of Hygiene* 54, no. 1 (March 1956): 49–57.

> ID_{10} is likely about 10 organisms as 9 out of 10 organisms are usually killed by the serum complement killing process and so the bottom number is about this. (Gary Splitter, *Brucella* conference, 1992?). Based on their monkey data, it looks like the ID_{90} is about 20 organisms (Richard Borsche [sic], *Brucella* conference, 1997).[589]

It appears that the results presented at the various Brucella conferences have been interpreted to mean that if 20 organisms are inhaled and 90% of those are either not retained or killed in the body (as they were in the serum-complement killing process), then the ID_{50} must be rather low.

During the course of our literature search, many documents were obtained and reviewed for information relevant to the infectivity of inhaled *Brucella* organisms. Quantitative estimates of the infective dose for humans via aerosol exposure were almost universally reported as 10 to 100 organisms, yet only 1 source indicated the origin of its estimate:

> The low yield of brucellae from kill department air and the evidence that airborne transmission of infection does occur suggest that the minimum infecting dose by the respiratory route is low for humans. The minimum oral infective dose of *B. abortus* and *B. suis* for guinea pigs is about 10^6 to 10^7 organisms; experimental evidence suggests a comparable minimum oral infective dose for humans. The minimum infecting dose by aerosol or subcutaneous injection of guinea pigs, however, is less than 100 organisms. If a comparable disparity exists for humans, the minimum respiratory infecting dose may also be less than 100 organisms.[590]

Deriving infectivity estimates by analogy with an animal model is not uncommon, but it is preferable to use an animal model more relevant than guinea pigs. NHPs have been found to be "an excellent model of human brucellosis,"[591] and our literature review identified six sources of information on brucellosis inhalation studies that used NHPs as the animal model—these sources are the basis for the *AMedP-7.5* model.

In the earliest of the six reports, a 1941 article by Meyer and Eddie,[592] the authors state that "unpublished experiments by Fleishner and Meyer support the early tests of Horrocks which showed that *B. melitensis* when present in dust may readily infect

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589 Anno et al., *AMedP-8* (*Biological*) *Methods Report*, 288.

590 Arnold F. Kaufmann et al., "Airborne Spread of Brucellosis," *Annals of the New York Academy of Sciences* 353, no. 1 (December 1980): 105–14.

591 Samuel L. Yingst, et al., "A Rhesus Macaque (*Macaca mulatta*) Model of Aerosol-Exposure Brucellosis (*Brucella suis*): Pathology and Diagnostic Implications," *Journal of Medical Microbiology* 59 (2010): 724–30.

592 K. F. Meyer and B. Eddie, "Laboratory Infections Due to Brucella," *The Journal of Infectious Diseases* 68, no. 1 (January-February 1941): 24–32.

monkeys." Although the results of the more recent studies were not published, Horrocks's experimental results were traced to a 1906 report[593] of the commission on "Mediterranean fever" led by Colonel David Bruce (after whom this disease was later renamed brucellosis). Horrocks reported (p. 46–48) that a caged monkey exposed to aerosolized dust particles infected with *B. melitensis* once a day for 22 days over the course of a month developed brucellosis. Unfortunately, as the monkey was exposed repeatedly to an unknown amount of agent, these results prove only that it is possible to infect a monkey through inhalation of infected dust particles, but provide no insight on a dose-response relationship.

In contrast, the experiment by Elberg et al. published in 1955 provides enough information to develop a quantitative dose-response model. Vaccinated and unvaccinated groups of RMs were exposed to aerosolized *B. melitensis*.[594] For the unvaccinated group, the article cites an ID_{50} of 1.3×10^3 organisms. We evaluated the same data (analysis not shown) using probit analysis and calculated a probit slope of 2.10 probits/log (dose) and an ID_{50} of 1.25×10^3 organisms, which is consistent with the value reported by Elberg et al. The same paper also reports that 10 of 10 control monkeys were infected and became ill after receiving an inhaled dose calculated to contain 3.6 ID_{50} of the same strain, which corresponds to 4,680 organisms using the ID_{50} calculated by that study's authors.

Among the results of subsequent studies by Elberg et al. published in 1962[595] are those of an aerosol challenge of monkeys (*Cynomolgus philippinensis*) immunized subcutaneously. The five monkeys in the unvaccinated control group all became infected (and presumably ill, although it is not clear from the article) after receiving an inhaled dose of 10,000 cells, a result that is consistent with Elberg's earlier findings, if cells are assumed to be equivalent units to organisms. In yet another study by Elberg et al. in 1964, 800 *B. melitensis* organisms were administered via the aerosol route to six macaques used as controls in a vaccine study.[596] Among these six macaques, the challenge dose produced localized infection in five and generalized infection and positive blood cultures in three.

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593 "Part IV," *Reports of the Commission Appointed by the Admiralty, the War Office, and the Civil Government of Malta, for the Investigation of Mediterranean Fever, Under the Supervision of an Advisory Committee of the Royal Society* (London: Harrison and Sons, February 1906).

594 Sanford S. Elberg et al., "Immunization against *Brucella* Infection: IV. Response of Monkeys to Injection of a Streptomycin-Dependent Strain of *Brucella melitensis*," *The Journal of Bacteriology* 69, no. 6 (June 1955): 643–648.

595 Sanford S. Elberg and W. K. Faunce, Jr., "Immunization against *Brucella* Infection. 8. The Response of *Cynomolgus philippinensis*, Guinea-Pigs and Pregnant Goats to Infection by the Rev I Strain of *Brucella melitensis*," *Bulletin of the World Health Organization* 26, no. 3 (1962): 421–436.

596 Sanford S. Elberg and W.K. Faunce, Jr., "Immunization against *Brucella* Infection. 10. The Relative Immunogenicity of *Brucella abortus* Strain 19-BA and *Brucella melitensis* Strain Rev

More recently, Mense et al. sought to develop a NHP model for inhalation exposure to *B. melitensis* in hopes of later evaluating candidate vaccines against brucellosis.[597] The respiratory doses (included in Table 155) administered to 10 RMs (including 2 controls that were not intentionally exposed) were recorded and blood samples taken weekly to determine the number of organisms per milliliter of blood. The authors report that six of the eight inoculated macaques were bacteremic and became ill. Although the monkeys inhaling 125 and 255 organisms were not bacteremic, nor did they test positive for bacterial culture in any of the tissue samples collected during necropsy, the authors claim that "both macaques challenge exposed with the lowest dose of inoculums contracted brucellosis."[598]

Note that both control monkeys also appear to have been infected, most likely via reaerosolization of *B. melitensis* organisms from exposed monkeys despite careful air washing of their fur. "[One] macaque [had] positive test results for bacterial culture of blood samples and spleen tissues and the other macaque [developed] antibody titers, indicating infection but to a differing degree."[599] Such findings may call into question the accuracy of the measured doses received by the other monkeys, but we assumed that the documented physiological effects are the result of inhaling the doses listed in Table 155.

The results of the above study are referenced in two other documents,[600] both of which are book chapters written by Hoover and Borschel, two of the coauthors of the Mense et al. article. Both book chapters summarize the Mense et al. data and also recount unpublished observations by the authors of four additional monkeys challenged via aerosol with 1×10^7 organisms, all of which became bacteremic.

Note that Richard Borschel, the researcher cited by the *P-8 BMR* as a source for the KAMI estimated ID_{90} of 20 organisms, is a coauthor on each of the three reports of the above data, which indicate an ID_{50} of 10^2–10^3 organisms for aerosol exposure to monkeys.

The final article with information regarding inhalation exposure of monkeys, published in 2010, describes an experiment by Yingst et al. in which 12 RMs were exposed

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I in *Cynomolgus philippinensis*," *Bulletin of the World Health Organization* 30, no. 5 (1964): 693–699.

597 M. G. Mense et al., "Pathologic Changes Associated with Brucellosis Experimentally Induced by Aerosol Exposure in Rhesus Macaques (*Macaca mulatta*)," *American Journal of Veterinary Research* 66, no. 5 (May 2004): 644–652.

598 Ibid., 650.

599 Ibid., 650.

600 David L. Hoover and Richard H. Borschel, "Medical Protection against Brucellosis," in *Infectious Diseases: Biological Weapons Defense: Infectious Diseases and Counterbioterrorism* , edited by L. E. Lindler, F. J. Lebeda and G. W. Korch (Totowa: Humana Press Inc., 2005); and David L. Hoover et al., "Development of New *Brucella* Vaccines by Molecular Methods," in *Brucella: Molecular and Cellular Biology*, edited by Ignacio López-Goñi and Ignacio Moriyón (Norwich: Horizon Bioscience, 2004).

via aerosol to high doses of *B. suis*.[601] Unfortunately, individual dose data were not provided, so the data could not be used.

A meta-analysis was performed using the monkey data presented above (and summarized in Table 155) under the assumption that one organism and one cell were equivalent units. We assumed that in the 1964 Elberg data, the three monkeys with generalized infections were a subset of the five with localized infections and one monkey remained infection-free. Since the two control monkeys in the Mense study likely inhaled an unknown, nonzero dose of agent, they were excluded from the dataset. Despite the authors' statement to the contrary, the two monkeys receiving doses of 10^2 organisms (125 and 255) were considered to be free of infection, as evidenced by their lack of bacteremic response and their negative tissue cultures in the data reported in the article.

Table 155. RM Data for Aerosol Exposure to *Brucella* Organisms

Inhaled Dose (organisms)	RMs Exposed	RMs Ill	Source
125	1	0	Mense 2004
255	1	0	Mense 2004
600	10	3	Elberg 1955
800	6	5	Elberg 1964
954	10	4	Elberg 1955
1,520	10	5	Elberg 1955
3,040	1	1	Mense 2004
3,600	1	1	Mense 2004
4,680	10	10	Elberg 1955
10,000	5	5	Elberg 1962
14,500	10	10	Elberg 1955
96,000	1	1	Mense 2004
102,000	1	1	Mense 2004
122,000	8	8	Elberg 1955
145,000	1	1	Mense 2004
334,000	1	1	Mense 2004
10,000,000[a]	4	4	Hoover 2004; Hoover 2005

[a] This data point was excluded in the final analysis for the reason described below.

601 Yingst et al., "A Rhesus Macaque (*Macaca mulatta*) Model of Aerosol-Exposure Brucellosis."

Probit analysis was used to evaluate the dataset shown in Table 155. Ultimately, the challenge dose of 10^7 organisms reported in the two book chapters was excluded from the final analysis because the dose was so much greater than the rest of the doses that its inclusion caused an error early in the iterative procedure before a proper fit could be confirmed through convergence. Without this data point, the data in Table 155 were best fit by a probit slope of 2.58 probits/log (dose) and an ID_{50} of 949 organisms.

This infectivity model is vastly different from that given in the *P-8 BMR*, with a median infective dose nearly 70 times higher and a probit slope of less than one-third the reference value. The ID_{50} value reflects the decision to rely on monkey inhalation exposure data, rather than a combination of guinea pig data and unpublished monkey data. The relatively shallow slope starkly contrasts the steep slope generated by ID_{10} and ID_{90} values of 10 and 20 organisms, respectively, and is reflective of the fact that the dataset includes four different doses between 255 and 3,040 organisms that infected only some of the monkeys exposed.

Lethality

Although brucellosis can occasionally be fatal, this is very rare and generally only occurs when the infection resides in the central nervous system or endocardium.[602] Although most brucellosis-induced endocarditis patients die without treatment,[603] this condition occurs in a very small percentage of cases, usually between 1 and 2%.[604] The occurrence of fatalities overall is universally reported to be low, with most references giving a rate below 6%. Yet because a large number of symptomatic individuals are never included in the case fatality rate statistics due to underreporting and misdiagnosis, an even lower probability of death from brucellosis results.

The *P-8 BMR* reports an untreated lethality of less than 5% overall, with specific fatality rates of 3% for *B. abortus* and 6% for *B. suis* and *B. melitensis*, whereas *MABW* does not specify a fatality rate. The published literature supports a low mortality for both treated and untreated cases. In the era before antibiotic treatment, case fatality rates were reported in several studies. In 1930, Hardy reports that 3 of 129 (2.3%) patients in Iowa died.[605] That same year, Simpson's article reported that 1 of 90 (1.1%) cases from Ohio

602 Purcell, Hoover, and Friedlander, "Brucellosis."

603 Jacobs et al., "Brucella Endocarditis: The Role of Combined Medical and Surgical Treatment."

604 M. R. Hasanjani Roushan et al., "Epidemiological Features and Clinical Manifestations in 469 Adult Patients with Brucellosis in Babol, Northern Iran," *Epidemiology and Infection* 132, no. 6 (2004): 1109–14.

605 A. V. Hardy et al., "Undulant Fever," *Public Health Reports* 45, no. 41 (October 10, 1930): 2433–74.

were fatal.[606] According to Gilbert's 1934 study of cases in New York, there were 6 fatalities in 400 cases (1.5%).[607] A few years later, Baltzan published an article describing 57 cases of brucellosis, of which 1 (1.8%) died, although this patient also had an enlarged liver and serious anemia before contracting brucellosis.[608] Combining these datasets yields an overall case fatality rate of less than 2%. Other accounts provide estimates for the untreated fatality rate of up to 6%.[609] Treated patients have an even higher likelihood of survival.[610]

In addition to the already low lethality figures derived from case fatality rates, several studies have demonstrated that brucellosis is vastly underreported or misdiagnosed, likely due to the nonspecific symptoms. One study, published in 1949 by Stoenner et al.,[611] concluded that for every brucellosis case reported in Utah, there are approximately 26 unreported cases. This finding is corroborated by other reports, which have determined the reporting rate of brucellosis to be less than 10%.[612] Since the untreated case fatality rate is likely less than 2% and is almost certainly no greater than 6%, and since most cases are misdiagnosed or unreported, it seems best to consider the CFR for brucellosis to be 0%.

Incubation Period

Because the brucellosis literature was found to contain ample data from human inhalation cases, animal data and human data for routes of exposure other than inhalation

606 W. M. Simpson, "Undulant Fever (Brucelliasis): A Clinicopathologio Study of Ninety Cases Occurring in and About Dayton, Ohio," *Annals of Internal Medicine* 4, no. 3 (1930): 238–259.

607 Ruth Gilbert and Marion B. Coleman, "Undulant Fever in New York State," *The Journal of Infectious Diseases* 54, no. 3 (May-June, 1934): 305–312.

608 D. M. Baltzan, "Experience with Fifty-Seven Brucellosis Infections in Saskatchewan," *The Canadian Medical Association Journal* 36, no. 3 (1937): 258–262.

609 P. W. Bassett-Smith, "Mediterranean or Undulant Fever," *The British Medical Journal* 2, no. 3228 (1922): 902–905; Alice C. Evans, "Undulant Fever," *The American Journal of Nursing* 30, no. 11 (1930): 1349–1352; Louise Hostman, "Undulant Fever," *The American Journal of Nursing* 34, no. 8 (1934): 753–758; P. Bossi et al.,"Bichat Guidelines for the Clinical Management of Brucellosis and Bioterrorism- Related Brucellosis," *Eurosurveillance* 9, no. 12 (2004): 1–5; and Pablo Yagupsky and Ellen Jo Baron, "Laboratory Exposures to Brucellae and Implications for Bioterrorism," *Emerging Infectious Diseases* 11, no. 8 (2005): 1180–1185.

610 Marshall D. Fox and Arnold F. Kaufmann, "Brucellosis in the United States, 1965–1974," *The Journal of Infectious Diseases* 136, no. 2 (1977): 312–316; Jacobs et al., "Brucella Endocarditis; M. J. Corbel, *Brucellosis in Humans and Animals* (Geneva, Switzerland: World Health Organization, 2006); and Sascha Al Dahouk et al., "Changing Epidemiology of Human Brucellosis, Germany, 1962–2005," *Emerging Infectious Diseases* 13, no. 2 (2007): 1895–1900.

611 Herbert G. Stoenner, Alton A. Jenkins, and E. H. Bramhall, "Studies of Brucellosis in Utah," *The Journal of Infectious Diseases* 85, no. 3 (1949): 213–224.

612 Robert I. Wise, "Brucellosis in the United States: Past, Present, and Future," *The Journal of American Medical Association* 244, no. 20 (1980): 2318; and Al Dahouk et al., "Changing Epidemiology of Human Brucellosis, Germany, 1962–2005," 1898.

are not considered. Although the human inhalation studies lack dose-response information, such information would only be available from a research program involving intentional exposure, and we are not aware of any such program in history for brucellosis.

The incubation period associated with brucellosis is highly variable, with reports ranging from a few days to many months. *AMedP-8* (*Biological*) *Methods Report* provides a dose-dependent incubation period model with a 35-day incubation period for individuals becoming ill after inhaling one organism and a 5-day incubation period for those inhaling 1 million organisms. The report states that incubation times are often much longer than this, about 2 weeks to 6 months, but decided that a shorter incubation time would better represent an attack scenario.[613] It is not unreasonable to assume that those individuals nearest the point of aerosol attack would inhale very high doses, which may result in shorter incubation periods. Nevertheless, such an attack would result in a distribution of doses from very high to very low, and a dose-dependent incubation period model should be independent of the distribution of doses received in a specific scenario.

A review of the literature revealed the extent to which the incubation period is known to vary. The incubation period is often difficult to characterize in large part because the exact date or dates of exposure are either unknown or span a considerable time. We extracted data on 74 cases of inhalation exposures from 11 reports of laboratory outbreaks or isolated accidents. Nine of these articles described cases caused by *B. melitensis*; one article, written by Fiori et al.,[614] characterized an incident of exposure to *B. abortus*; and one, composed by Trever et al.,[615] reported a combination of cases caused by *B. melitensis* and *B. suis*. Since the incubation periods were similar following exposure to any of these three species, all were used in a meta-analysis under the assumption that the incubation period is independent of the species of *Brucella* organism. In some cases, interpretation of the data from these 11 articles was necessary before they could be incorporated. For instance, the majority of incubation periods were reported in units of weeks, so those expressed in other units were rounded to the nearest whole week for the sake of a consistent level of precision in the dataset.

Here we summarize the reports and describe any data manipulation we performed in generating the data found in Table 158.

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613 Anno et al., *AMedP-8* (*Biological*) *Methods Report*, 206–207.

614 Pier-Luigi Fiori et al., "*Brucella abortus* Infection Acquired in Microbiology Laboratories," *Journal of Clinical Microbiology* 38, no. 5 (May 2000): 2005–2006.

615 Robert W. Trever et al., "Brucellosis I. Laboratory-Acquired Acute Infection," *American Medical Association Archives of Internal Medicine* 103, no. 3 (March 1959): 381–397.

The earliest report found to contain incubation period data for inhalation exposures was a 1959 article written by Trever et al. summarizing 60 cases of acute brucellosis.[616] For 21 of these patients, a specific laboratory accident was known to have occurred before symptom onset, from which the incubation period was determined. Rather than listing the incubation period for each particular case, however, the article provided the frequency of patients within one of six ranges of incubation periods, as shown in the first two columns of Table 156. To use these data, the cases within each range were assumed to be distributed evenly across that range. For instance, six individuals fell within the incubation period range spanning 2 to 4 weeks, so this range was divided into six even intervals, and one case was assumed to occur at the end of each interval. To match the precision of the meta-dataset, these values were rounded to the nearest whole week value as shown in the last column of Table 156. This distribution of the 21 cases results in a mean incubation period of 6.05 weeks, which is consistent with the mean value reported by Trever et al. of 6 weeks.

Table 156. Trever et al. Incubation Period Data

Case #	Incubation Period Range (weeks)	Distributed Incubation Period (weeks)	Rounded Incubation Period (weeks)
1	0–1	0.50	1
2	0–1	1.00	1
3	1–2	1.50	2
4	1–2	2.00	2
5	2–4	2.33	2
6	2–4	2.67	3
7	2–4	3.00	3
8	2–4	3.33	3
9	2–4	3.67	4
10	2–4	4.00	4
11	4–8	4.57	5
12	4–8	5.14	5
13	4–8	5.71	6
14	4–8	6.29	6
15	4–8	6.86	7
16	4–8	7.43	7
17	4–8	8.00	8
18	8–16	10.67	11
19	8–16	13.33	13

616 Ibid.

Case #	Incubation Period Range (weeks)	Distributed Incubation Period (weeks)	Rounded Incubation Period (weeks)
20	8–16	16.00	16
21	16–18	18.00	18

In 1983, Young reported 10 cases of brucellosis,[617] the majority of which resulted from ingestion of contaminated dairy products or from an unknown source. Three laboratory-acquired cases, however, were presumed to be inhalation exposures. Only one of these patients (Case 3) experienced an overt contamination, which occurred when he accidentally sprayed his face with a suspension of *B. melitensis*, leading to symptoms approximately 4 weeks later. Incubation periods for the other two cases were unspecified.

Twenty-two cases of acute brucellosis infection in Spain were reported by Olle-Goig and Canela-Soler in their 1987 article.[618] Laboratory personnel were assumed to have been exposed during the manufacturing of a brucellosis vaccine during the first week of June 1982, and their symptom onset was recorded by week, with cases appearing from 6 to 15 weeks after exposure.

Another four cases were reported from Saudi Arabia by Al-Aska and Chagla in 1989. "Case 1 probably acquired infection by direct inhalation, as well as by mucus membrane contact with the organism due to splashing on the face from a positive culture bottle. Cases 2 and 3 acquired infection probably by inhaling contaminated aerosols while working on an open bench. Case 4 acquired infection by needlestick injury to the hand from a needle containing synovial fluid from a patient with brucellosis."[619] Cases 1 and 4 were disregarded because the route of exposure was not solely inhalation, and the Case 3 description included no information on the incubation period. Only the value of 2 weeks reported for Case 2 was included among the data used in the incubation period submodel.

In their 1991 article, Staszkiewicz et al. reported that in the last 2 days of March 1988, a frozen *Brucella* isolate was thawed and handled on an open workbench, exposing at least eight individuals who later developed brucellosis.[620] The first case manifested approximately 6 weeks after this presumed exposure, while the remaining seven cases were

617 Edward J. Young, "Human Brucellosis," *Reviews of Infectious Diseases* 5, no. 5 (1983): 821–842.

618 Jaime E. Olle-Goig and and Jaime Canela-Soler, "An Outbreak of *Brucella melitensis* by Airborne Transmission Among Laboratory Workers," *American Journal of Public Health* 77, no. 3 (March 1987): 335–338.

619 Abdul Karim Al-Aska and Abdul Hamid Chagla, "Laboratory-Acquired Brucellosis," *Journal of Hospital Infection* 14, no. 1 (1989): 70–71.

620 Staszkiewicz et al., "Outbreak of *Brucella melitensis* among Microbiology Laboratory Workers in a Community Hospital."

described only by the month of onset. For these seven cases, the dates of symptom onset were distributed evenly across the month, as was done above for the Trever et al. data. Table 157 shows the raw data presented in the Staszkiewicz et al. article, along with the assumed dates of onset and the corresponding incubation period in weeks after the exposure date of March 31, 1988.

Table 157. Staszkiewicz et al. Incubation Period Data

Case #	Month of Onset	Distributed Dates of Onset	Rounded Incubation Period (weeks)
1	May	N/A[a]	6
2	June	15-Jun-88	11
3	June	30-Jun-88	13
4	July	31-Jul-88	17
5	August	10-Aug-88	19
6	August	20-Aug-88	20
7	August	31-Aug-88	22
8	September	30-Sep-88	26

[a] The article explicitly stated a 6-week incubation period for this case.

Gruner et al.[621] report five cases of laboratory-acquired brucellosis, of which three characterize the incubation period. Two lab technicians (Cases 3 and 5) first developed symptoms 2 months after working with strains of *Brucella* from an infected patient, and one (Case 4) presented to the hospital 4 months after contact with the same strain. By rounding the number of days in 2 and 4 months to the nearest number of weeks, we included these three cases as data points at 9 and 17 weeks.

In 2000, Fiori et al. reported an outbreak of brucellosis among 12 laboratory workers resulting from a known accidental exposure, with incubation times "ranging from six weeks to five months."[622] The exact dates of symptom onset were given for seven workers, and for the remaining five individuals, only the dates of their first positive antibody titers indicating infection were provided. The authors were less specific, however, when reporting the date of exposure, stating simply that it occurred during the first week of October 1990.

Using the seven cases with known dates of symptom onset, an analysis was conducted to determine the sensitivity of the incubation periods to a variable exposure date ranging

621 Gruner et al., "Brucellosis: An Occupational Hazard."

622 Fiori et al., "*Brucella abortus* Infection Acquired in Microbiology Laboratories," 2005.

from Monday to Friday. When values were rounded to whole weeks, the set of seven incubation periods was the same for exposure dates of Tuesday through Thursday. Since Wednesday, October 3, 1990, was representative of the majority of the workdays and it was the middle of the week, it was assumed that this day would best approximate the actual exposure date.

To use the five cases without specific dates of symptom onset, an assumption would have to be made regarding the time between the first positive antibody titer and the onset of symptoms. For the four patients (among the first seven) for whom both dates were known, this time ranged from two to five days. Therefore, it was assumed that the remaining five individuals would likewise manifest symptoms at some time during that range of days after the first positive anti-*Brucella* titer. It was determined through another sensitivity analysis that for an October 3 exposure date, the incubation periods were not sensitive (to the level of weeks) to the difference between two and five days. In other words, using either end of the range resulted in the same estimates for incubation period, when rounding to the nearest whole-week value. We incorporated all 12 cases under the above assumptions.

Seven cases are reported by Memish and Mah from Saudi Arabia in 2001.[623] The time of exposure was known with relative confidence only in two cases (Case 2 and Case 3). In Case 2, a microbiology technologist became ill 13 weeks after sniffing a specimen later proven to be *B. melitensis*. In Case 3, another technologist developed symptoms 18 days (rounded to three weeks) after thawing samples of *Brucella* isolates to check their viability. The remaining cases were excluded because either no known date of exposure was described or else two possible exposure periods were provided, creating uncertainty in the correct duration of the incubation period.

The two cases of brucellosis described in the 2004 article by Noviello et al.[624] resulted from the misidentification of positive blood cultures and their subsequent handling without the proper safety precautions. In the first case, a laboratory worker processed a patient's blood culture specimen on an open bench, and approximately 5 weeks later, she become symptomatic. Upon her admission to the hospital, a blood culture specimen was taken and subsequently examined by a second lab worker under the same working conditions, who similarly developed illness 2 months (9 weeks) later.

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623 Ziad A. Memish and M. W. Mah, "Brucellosis in Laboratory Workers at a Saudi Arabian Hospital,"*American Journal of Infection Control* 29, no. 1 (2001): 48–52.

624 Stephanie Noviello et al., "Laboratory-Acquired Brucellosis," *Emerging Infectious Diseases* 10, no. 10 (2004): 1848–50.

Twenty-six laboratory workers were potentially exposed in the accident described by Robichaud et al. in their 2004 article.[625] Ten weeks after the exposure, one individual who had refused antibiotic prophylaxis became symptomatic, while the remaining individuals remained symptom free.

In the final and most recent case report of laboratory-acquired brucellosis, Demirdal and Demirturk describe three cases of exposure to the same *Brucella* samples, although only for one of the three workers was the time of exposure given relative to the onset of symptoms.[626] In this case, the contact with the samples occurred 2 weeks before symptom onset.

Table 158. Summary of 74 Cases of Laboratory Acquired Inhalation Brucellosis in Humans

Case #	Incubation Period (weeks)	Case #	Incubation Period (weeks)	Case #	Incubation Period (weeks)
Trever 1959		**Olle-Goig 1987**		**Gruner 1994**	
1	1	6	7	1	9
2	1	7	8	2	9
3	2	8	8	3	17
4	2	9	9	**Fiori 2000**	
5	2	10	10	1	6
6	3	11	10	2	6
7	3	12	10	3	6
8	3	13	11	4	10
9	4	14	11	5	10
10	4	15	13	6	10
11	5	16	13	7	10
12	5	17	13	8	11
13	6	18	13	9	14
14	6	19	14	10	14
15	7	20	14	11	14
16	7	21	15	12	24
17	8	22	15	**Memish 2001**	
18	11	**Al-Aska 1989**		1	3

625 Sophie Robichaud et al., "Prevention of Laboratory-Acquired Brucellosis," *Clinical Infectious Diseases* 38, no. 12 (June 15, 2004): e119–22.

626 Tuna Demirdal and Nese Demirturk, "Laboratory-Acquired Brucellosis," *Annals Academy of Medicine* 37, no. 1 (2008): 86–87.

Case #	Incubation Period (weeks)	Case #	Incubation Period (weeks)	Case #	Incubation Period (weeks)
19	13	1	2	2	13
20	16	**Staszkiewicz 1991**		**Noviello 2004**	
21	18	1	6	1	5
Young 1983		2	11	2	9
1	4	3	13	**Robichaud 2004**	
Olle-Goig 1987		4	17	1	10
1	6	5	19	**Demirdal 2008**	
2	6	6	20	1	2
3	7	7	22		
4	7	8	26		
5	7				

Note: See Appendix B for full reference citations.

The 74 data points from the 11 articles described in this section are summarized in Table 158. The range of incubation period durations in this dataset extends from 1 to 26 weeks, with the middle 50% of cases manifesting symptoms between 6 and 13 weeks after exposure. Several distributions were fit to the data using @RISK software,[627] and the root-mean-square error was used to determine the most appropriate model. By this measure, a Weibull distribution with a mean of 9.09 weeks and standard deviation of 5.45 weeks was the found to be the best fit. The characteristic parameters for this Weibull distribution are shape parameter (k) = 1.72 (unitless) and scale parameter (θ) = 10.2 weeks. Since *AMedP-7.5* uses a reporting resolution of days, the parameters with units of weeks are converted to days by simply multiplying each by 7: mean of 63.63 days, standard deviation of 38.15 days, k = 1.72 (not converted because it is unitless) and θ = 71.4 days.

A final note: while we understand that the incubation period may indeed be dose-dependent (which may help explain the wide range of incubation periods), without quantitative dose estimates from any of the cases considered, we could not derive a dose-dependent model.

Injury Profile

The symptoms of brucellosis, although nonspecific in nature, are well characterized in the literature. Several review articles have summarized hundreds of cases used to

627 *@Risk for Excel: Risk Analysis Add-in for Microsoft Excel*, Version 5.5.1: Professional Edition (Palisade Corporation, 2010).

develop lists of symptoms and their rates of incidence among brucellosis patients.[628] Overall, the presentation of symptoms appears to be independent of the route of exposure[629] as well as the species of *Brucella* organism.[630] The symptoms and progression of symptoms may vary from one patient to the next. Brucellosis cases are classically categorized, based on the duration of symptoms, as acute (less than 2 months), subacute (2 months to 1 year), or chronic (greater than 1 year),[631] although this classification has been criticized as subjective and of limited clinical interest.[632] Regardless of the duration of illness, the onset of disease can be broadly characterized as either abrupt or insidious, so two separate Injury Profiles have been developed to reflect the variable symptom presentations.

MABW describes the symptoms of disease as nonspecific, "such as fever, sweats, fatigue, anorexia, and muscle or joint aches."[633] Similarly, the *P-8 BMR* states that "somatic complaints dominate, with fever, malaise, sweats, headaches, arthralgias, myalgia (particularly in the lower back), anorexia, and weight loss among the symptoms most commonly reported. Other symptoms include chills, asthenia, nausea, vomiting, and constipation."[634] Combining the descriptions from these two documents, we have chosen a symptom complex of fever, sweats, chills, headache, malaise, fatigue, arthralgia, myalgia, anorexia, and weight loss to represent this disease.

According to *MABW*, the disease may be abrupt or insidious in onset.[635] The following description by Hardy illustrates the extent to which the two extreme manifestations of symptom onset can vary:

> So mild were the symptoms in some of the cases that it became a matter of nice discrimination to distinguish the sick man from the mere pretender. On the other hand, the patient sometimes appeared to have been completely prostrated at once by the severity of the onset. However, in many of these the suddenness of the attack was more apparent than real, for a careful

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628 Fox and Kaufmann, "Brucellosis in the United States, 1965–1974," Corbel, *Brucellosis in Humans and Animals*; Mehmet Doganay and Bilgehan Aygen, "Human Brucellosis: An Overview," *International Journal of Infectious Diseases* 7, no. 3 (2003): 173–182; Roushan et al., "Epidemiological Features and Clinical Manifestations in 469 Adult Patients with Brucellosis in Babol, Northern Iran," and Abdul Rahman M. Mousa et al., "The Nature of Human Brucellosis in Kuwait: Study of 379 Cases," *Reviews of Infectious Diseases* 10, no. 1 (1988): 211–17.

629 Purcell, Hoover, and Friedlander, "Brucellosis," 189.

630 Georgios Pappas et al., "Brucellosis," *The New England Journal of Medicine* 352, no. 22 (2005): 2330.

631 A. R. Lulu et al., "Human Brucellosis in Kuwait: A Prospective Study of 400 Cases," *Quarterly Journal of Medicine* 66, no. 249 (1988): 39–54.

632 Pappas et al., "Brucellosis," 2329.

633 Purcell, Hoover, and Friedlander, "Brucellosis," 189.

634 Anno et al., *AMedP-8* (*Biological*) *Methods Report*, 42.

635 Purcell, Hoover, and Friedlander, "Brucellosis," 189.

> inquiry often revealed a previous stage of dyspepsia, debility, and languor.[636]

Reports have shown that the distribution of these cases is split more or less equally, with approximately half the cases taking ill rather suddenly.[637] A review of these cases described above for the incubation period submodel and some additional pre-antibiotic-era case reports that did not include incubation period data[638] turned up 23 cases of brucellosis with a gradual onset and 21 cases which were interpreted as having an abrupt onset, which supports the assumption that the split is roughly even.

As indicated by its former name of "undulant fever," brucellosis is characterized by an irregular febrile pattern that often fluctuates during the day, with temperature typically peaking during the late afternoon or evening.[639] In one review of 1,288 cases, fever was intermittent in 83% of cases with course of fever specified.[640] The undulation can also refer to alternating periods of fever and apyrexia lasting days, weeks, or months that patients sometimes experience.

Such recurring febrile relapses are often seen in brucellosis patients within the first 6 months after therapy.[641] The relapse symptoms typically mirror those of the initial illness, but are often milder than the original. In one study of human brucellosis cases in Kuwait, 41.4% of patients relapsed within 6 months of completing antibiotic treatment.[642] In another study of laboratory outbreaks, 5 of the 17 patients had no relapses, 9 had one relapse, 2 had two relapses, and 1 had four relapses.[643] It is possible that the high rates of relapse in these two studies are related to the choices or application of treatment, as

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636 Hardy et al., "Undulant Fever," 2435.

637 Young, "Human Brucellosis," Edward J. Young, "An Overview of Human Brucellosis," *Clinical Infectious Diseases* 21, no. 2 (1995): 283–289; and Bossi et al., "Bichat Guidelines for the Clinical Management of Brucellosis and Bioterrorism-Related Brucellosis."

638 Ruth Gilbert and Marion B. Coleman, "Recent Cases of Undulant Fever in New York State," *The Journal of Infectious Diseases* 43, no. 4 (1928): 273–277; George E. Atwood and H.E. Hasseltine, "Undulant Fever in Ware County, Ga," *Public Health Reports* (*1896–1970*) 45, no. 24 (June 13, 1930): 1343–1354.; A. Geoffrey Shera, "Four Cases of Undulant Fever," *The British Medical Journal* 2, no. 3691 (October 3, 1931): 605–607.; and A. V. Hardy, S. Frant, and M. M. Kroll, "The Incubation Period in Undulant Fever," *Public Health Reports* 53, no. 20 (1938): 796–803.

639 Philip Manson-Bahr and Hugh Willoughby, "A Critical Study of Undulant Fever," *The British Medical Journal* 1, no. 3561 (1929): 633–35; Gilbert and Coleman, "Recent Cases of Undulant Fever in New York State," and Simpson, "Undulant Fever (Brucelliasis): A Clinicopathologio Study of Ninety Cases Occurring in and About Dayton, Ohio."

640 Fox and Kaufmann, "Brucellosis in the United States, 1965–1974."

641 Hardy et al., "Undulant Fever."

642 Mousa et al., "The Nature of Human Brucellosis in Kuwait," 211–217.

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

inappropriate or ineffective antibiotic therapy is a known risk factor for relapse.[644] In contrast, recurring undulations of fever occurred in only 11 of 90 cases (12%) reported by Simpson in 1930 before the widespread use of antibiotics, and the vast majority of patients experienced only one febrile period.[645]

Because relapses occur in a minority of untreated cases and it is sometimes unclear whether reported illness durations include single or multiple periods of illness, relapses will not be explicitly modeled. Studies reporting that the duration of illness spans two or more distinct episodes of illness surrounding a long period without symptoms were excluded. On the other hand, if the duration was indicated without an explicit statement that relapse was included, it was assumed that the symptoms persisted for the majority of that duration, although a short asymptomatic period may have occurred.

Two distinct Injury Profiles have been developed for brucellosis to reflect the two forms of disease onset. For 50% of individuals, brucellosis is modeled with only one stage of illness, which begins abruptly with symptoms of fever, sweats, chills, headache, malaise, fatigue, arthralgia, myalgia, anorexia, and weight loss. As shown in Table 159 this combination of symptoms is designated as Severity Level 3 ("Severe") since the majority of brucellosis patients are admitted to the hospital as inpatients. Although the symptoms often progress throughout the course of the day, diurnal undulations are ignored and a day during which severe symptoms are present in the evening is still considered a day of severe illness.

Table 159. Brucellosis Abrupt Onset Injury Profile

	Stage 1
Signs and Symptoms (S/S)	Fever, sweats, chills, headache, malaise, fatigue, arthralgia, myalgia, anorexia, weight loss
S/S Severity	3 (Severe)

For the remaining 50% of individuals, the disease is modeled with two stages. These individuals are expected to experience an illness with an insidious onset, so the illness has been divided into two stages. Individuals will first progress through a prodromal stage characterized by symptoms of a lesser severity. The 23 cases found to have an insidious onset offered no useful information regarding which symptoms constituted the initial complex. Atwood characterized the period in nine cases as either "vague" or "prodromal" symptoms. In another study, the differentiation was made between the time to the first

644 Javier Ariza et al., "Characteristics of and Risk Factors for Relapse of Brucellosis in Humans," *Clinical Infectious Diseases* 20, no.5 (May 1995): 1241–1249.

645 Simpson, "Undulant Fever (Brucelliasis)."

symptoms and the time to "severe" symptoms, although these terms were not defined in the text.[646]

Ultimately, we relied on the *P-8 BMR* when selecting the symptoms for this prodromal stage; the document indicates a 4-day period of "some fever and malaise."[647] Accordingly, we decided to characterize the first stage of illness in the insidious onset Injury Profile as Severity Level 1 ("Mild") to reflect the presence of fever and malaise. The full two-stage Injury Profile is shown in Table 160. This profile more closely resembles the Injury Profile detailed in the *P-8 BMR*, which models brucellosis as a disease that begins with mild symptoms and progresses steadily to more severe symptoms.

Table 160. Brucellosis Insidious Onset Injury Profile

	Stage 1	Stage 2
Signs and Symptoms (S/S)	Fever, malaise	Fever, sweats, chills, headache, malaise, fatigue, arthralgia, myalgia, anorexia, weight loss
S/S Severity	1 (Mild)	3 (Severe)

Duration of Illness

The duration of the illness is difficult to determine from recent literature since most publications report cases for which antibiotic treatment was provided soon into the illness. Several early papers provide either summary statistics on the distribution of illness duration or specific case histories detailing the course of illness. Such cases were used to determine both the total duration of illness for both Injury Profiles and also the duration of Stage 1 for the insidious onset Injury Profile.

MABW describes brucellosis as a disease of 3- to 6-month duration that occasionally persists for more than a year.[648] KAMI estimates, which are reported but never used in the *P-8 BMR*, indicate that the duration of illness could be lifelong without medical treatment, but approximately 6 weeks to several years with medical treatment.[649] Since both these estimates are based on patients who received treatment, they could not be used for the duration of illness model.

We found information on the duration of untreated brucellosis in six articles from the pre-antibiotic era. Three of these publications provided only summary statistics of their findings on many cases. In 1922, Bassett-Smith published a report summarizing 522 cases

646 Hardy, "The Incubation Period in Undulant Fever."
647 Anno et al., *AMedP-8* (*Biological*) *Methods Report*, 43.
648 Purcell, Hoover, and Friedlander, "Brucellosis," 189.
649 Anno et al., *AMedP-8* (*Biological*) *Methods Report*, 210.

of brucellosis from which he determined that the disease duration ranged from 2 weeks to 2 years, with an average of 4 months.[650] In a vaccination study by Hardy in 1930, the average duration of illness among 105 cases of unvaccinated controls was 33.9 days.[651] Last, Simpson studied 90 cases in Dayton, Ohio, and estimated the average duration of illness to be approximately 4 months.[652]

Another three studies provided actual case descriptions from which the duration of illness could be determined in some cases. Gilbert and Coleman report 26 cases of brucellosis in New York, although only the first four pages of the article could be obtained, which allowed access to 21 cases.[653] From these 21 case reports, 9 definitive durations of illness were obtained. In the case where a range of times was given, the midpoint was chosen, and all data points were rounded to weeks in the same manner as incubation period data. Atwood and Hasseltine published a summary of brucellosis in Ware County, Georgia, in 1930, summarizing nine cases, all of which had durations specified in weeks.[654] Finally, four additional cases were documented by Shera in 1931.[655] Table 161 shows the data extracted from these three sources, along with these values converted into whole-week values for use in analysis.

Table 161. Summary of Duration in 22 Cases of Brucellosis

Source	Case	Duration	Rounded Duration (weeks)
Gilbert 1928	1	4–5 months	20
———	2	2 weeks	2
———	3	4 months	17
———	4	10 weeks	10
———	5	2 months	9
———	6	3 months	13
———	7	3–4 weeks	4
———	8	5 weeks	5
———	9	3.5 months	15
Atwood 1930	1	4 weeks	4
———	2	8 weeks	8
———	3	8 weeks	8

650 Bassett-Smith, “Mediterranean or Undulant Fever,” 903.
651 Hardy et al., “Undulant Fever,” 2431.
652 Simpson, “Undulant Fever (Brucelliasis),” 248.
653 Gilbert and Coleman, “Undulant Fever in New York State.”
654 Atwood and Hasseltine, “Undulant Fever in Ware County, Ga.”
655 Shera, “Four Cases of Undulant Fever.”

Source	Case	Duration	Rounded Duration (weeks)
———	4	8 weeks	8
———	5	11 weeks	11
———	6	11 weeks	11
———	7	11 weeks	11
———	8	11 weeks	11
———	9	20 weeks	20
Shera 1931	1	16 weeks	16
———	2	9 weeks	9
———	3	9 weeks	9
———	4	7 weeks	7

Note: See appendix B for full reference citations.

The median and mean values from this dataset are 9.5 and approximately 10 weeks, respectively. We used @RISK software[656] to determine the best fit to these data, choosing a gamma distribution on the basis of the root-mean-square error. The distribution mean (10.1 weeks) and standard deviation (5.05 weeks) are consistent with the sample parameters. The specific gamma distribution parameters output by @RISK were $k = 3.97$ (unitless) and $\theta = 2.54$ weeks. Again converting from units of weeks to units of days: the mean is 70.7 days, the standard deviation is 35.35 days, $k = 3.97$ (unitless) and $\theta = 17.78$ days.

The duration of Stage 1 for the insidious onset Injury Profile was derived by reviewing cases from the three articles cited for the total duration, as well as from a 1938 report by Hardy on the incubation period. Hardy's publication provided two dates of symptom onset: one for the earliest symptoms and one for "severe" symptoms. The time between these two onsets can be interpreted as the duration of the prodromal period. The 20 cases of insidious onset from Hardy and the three older articles are listed in Table 162, and once again, the durations have been rounded to whole week values.

Table 162. Summary of Duration in 20 Insidiois Onset Cases of Brucellosis

Source	Case	Duration	Rounded Duration (weeks)
Gilbert 1928	1	8 days	1
Atwood 1930	1	8 days	1
———	2	4 weeks	4
———	3	2 months	9

656 *@Risk for Excel*.

Source	Case	Duration	Rounded Duration (weeks)
———	4	2 weeks	2
———	5	14 weeks	14
———	6	11 days	2
———	7	over 1 month	4
———	8	16 days	2
———	9	1 month	4
Shera 1931	1	10 days	1
Hardy 1938	1	6 days	1
———	2	21 days	3
———	3	7 days	1
———	4	41 days	6
———	5	123 days	18
———	6	50 days	7
———	7	46 days	7
———	8	23 days	3
———	9	52 days	7

Note: See appendix B for full reference citations.

As was done for the total duration of illness, we used @RISK software[657] to determine the duration of Stage 1 of the insidious onset Injury Profile from the above data. The mean duration of Stage 1 predicted by the model (4.41 weeks) and standard deviation (4.84 weeks) are reasonably close to the observed values (4.85 weeks and 5.57 weeks, respectively). The parameters of this gamma distribution as output by @RISK were k = 0.827 (unitless) and θ = 5.32 (weeks). Again converting from units of weeks to units of days: the model mean is 30.87 days, the standard deviation is 33.88 days, k = 0.827 (unitless), and θ = 37.24 days.

Medical Countermeasures and Treatment Model

Medical management of brucellosis focuses on reducing the duration of illness and preventing relapse through the administration of antibiotics. There is no commercially available vaccine for humans against brucellosis. Neither are there formal or consensus recommendations for antibiotic prophylaxis, although anecdotal evidence indicates that it may effectively prevent disease. In one incident of accidental laboratory exposure,[658] five out of six technicians who may have been exposed to brucellosis underwent antibiotic prophylaxis and never developed symptoms; the sixth technician refused antibiotics and

657 *@Risk for Excel.*

658 Robichaud et al., “Prevention of Laboratory-Acquired Brucellosis.”

developed symptomatic disease. Thus, antibiotic prophylaxis should be considered in the event of confirmed exposure to brucellosis. Given the sparsity of data on the efficacy post-exposure prophylaxis, however, it is not included in *AMedP-7.5*.

Treatment for brucellosis involves the administration of antibiotics and supportive care. Because therapy with a single antibiotic has resulted in a high relapse rate, combined regimens are generally recommended.[659] Although there is no standardized treatment regimen for brucellosis, a 6-week oral regimen of the drugs rifampin at 900 mg per day and doxycycline at 200 mg per day for 45 days has been shown to be nearly 100% effective in treating most clinical manifestations of brucellosis, with a relapse rate of less than 10%.[660] Other drug combinations may provide equal or better outcomes for patients with certain specific manifestations of illness, such as those with spondylitis or osteoarticular involvement.[661] Some studies have also suggested that adding a third antibiotic may provide an even higher cure rate and reduce relapse rates to near zero.[662]

The only submodel affected by the consideration of medical treatment is duration of illness. The disease has an extended course, even with treatment, and typically is severe enough to require a period of routine hospitalization. In one study of 379 brucellosis patients in Kuwait, the mean hospital stay was 9 days, with a range of 3 to 90.[663] Among these patients, different symptoms resolved at different times: arthralgia, myalgia, and sweats resolved within 7 days of the start of treatment; arthritis generally within 2 weeks; pulmonary signs and symptoms between 1 and 2 weeks; and the pain and muscle spasms associated with spondylitis within about 2 weeks, although patients with the latter manifestation did not see significant radiologic improvement for months. The resolution of fever was highly variable, with 19% of cases becoming afebrile before the initiation of treatment, 43% within 5 days of the start of treatment, 29% within 6 and 10 days, and 9% at periods longer than 10 days.

Although brucellosis is not a fatal disease, afflicted patients are considered severely ill and are assumed to require routine hospitalization for 2 weeks. After discharge, they will require outpatient care and the continued administration of antibiotics for an additional 4 weeks. These timelines are loosely informed by the data presented above, but ultimately were arbitrarily chosen.

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659 Purcell, Hoover, and Friedlander, “Brucellosis,” 191.

660 Recommendation of the Joint FAO/WHO Expert Committee on Brucellosis, *World Health Organization Technical Report Service* 740 (1986): 1–132. Cited in Purcell, Hoover, and Friedlander, “Brucellosis.”

661 Buzgan et al., “1028 Cases of Brucellosis,” e477.

662 See for example, Mousa et al., “The Nature of Human Brucellosis in Kuwait.”

663 Mousa et al., “The Nature of Human Brucellosis in Kuwait.”

We assume that the antibiotic therapy administered is an effective drug combination and for an effective duration, and the probability of relapse is therefore minimized. Because relapse in such circumstances would be expected in fewer than 10% of cases, it is not included in the model.

Model Summary

Table 163 through Table 165 summarize the recommended model parameters for brucellosis used in *AMedP-7.5*. While the parameters in these tables represent current best estimates, any new data that become available could be incorporated and may improve the model, particularly for the infectivity model, since the other models are based on human data.

Table 163. Brucellosis Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 949 organisms Probit slope = 2.58 probits/log (dose)
Lethality	Rate	0%
Incubation period	Weibull distribution	Mean = 63.63 days Standard deviation = 38.15 days α = 1.72, β = 71.4 days
Duration of illness		
• Stage 1 (insidious onset)	Gamma distribution	Mean = 30.87 days Standard deviation = 33.88 days k = 0.827; θ = 37.24 days
• Total Duration (insidious and abrupt onset)	Gamma distribution	Mean = 70.7 days Standard deviation = 35.35 days k = 3.97; θ = 17.78 days
• Total Duration after initiation of treatment	Constant	14 days
• Convalescence period after treatment	Constant	28 days

Table 164. Brucellosis Abrupt Onset Injury Profile

	Stage 1
Signs and Symptoms (S/S)	Fever, sweats, chills, headache, malaise, fatigue, arthralgia, myalgia, anorexia, weight loss
S/S Severity	3 (Severe)

Table 165. Brucellosis Insidious Onset Injury Profile

	Stage 1	Stage 2

Signs and Symptoms (S/S)	Fever, malaise	Fever, sweats, chills, headache, malaise, fatigue, arthralgia, myalgia, anorexia, weight loss
S/S Severity	1 (Mild)	3 (Severe)

Cohorts and Special Considerations (*AMedP-7.5 Section 5.2.2.3*)

The definitions of the cohorts are sufficiently explained in *AMedP-7.5*. This section explains the equations used to calculate the cohort populations; for definitions of the variables in the equations, see *AMedP-7.5*.

Equation 5-42:	The half of the population that is abrupt onset, multiplied by the fraction that has completed the duration of illness by $d_{trt\text{-}bruc}$
Equation 5-43:	The half of the population that is abrupt onset, multiplied by the fraction that has *NOT* completed incubation yet
Equation 5-44:	The half of the population that is abrupt onset, minus the populations calculated in the preceding two equations.
Equation 5-45:	The half of the population that is insidious onset, multiplied by the fraction that has completed the duration of illness by $d_{trt\text{-}bruc}$
Equation 5-46:	The half of the population that is insidious onset, multiplied by the fraction that has *NOT* completed incubation yet
Casualty criterion WIA(1^+) means that Stage 1 insidious onset causes casualties, and therefore people in Stage 1 will begin receiving treatment	
Equation 5-47:	The half of the population that is insidious onset, multiplied by the fraction that has completed Stage 1; to avoid double-counting, those who have completed Stage 2 are subtracted out.
Equation 5-48:	The half of the population that is insidious onset, minus the populations of all the other insidious onset cohorts
Casualty criterion WIA(2^+) or WIA(3^+) means that Stage 1 insidious onset does *NOT* cause casualties, and therefore only people in Stage 2 will receive treatment	
Equation 5-49:	The half of the population that is insidious onset, minus the populations of all the other non-zero insidious onset cohorts
Equation 5-50:	Zero because individuals in Stage 1 are not considered WIA according to the casualty criterion.

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1.21. Glanders Model
(*AMedP-7.5 Section 5.2.3*)

Introduction[664]

Glanders is a zoonotic disease of horses, mules, donkeys, and other solipeds caused by the bacteria *Burkholderia mallei* (*B. mallei*). It is an ancient disease, first described by Aristotle in 330 BC, and by the 19th-century glanders was fairly common in animals worldwide. Once diagnostic testing became available by the turn of the 20th century, eradication programs proceeded in earnest in many nations. The last naturally occurring human case of glanders in the United States was reported in 1934; the disease was officially eradicated from the United States in 1942. Today glanders has been eradicated from most countries, but is still found in parts of Africa, the Middle East, South America, and Eastern Europe.

Most human cases of glanders occur among individuals in occupational and lifestyle settings, such as veterinarians, farriers, slaughterhouse personnel, farmers, and stable hands. *B. mallei* can survive in a wide variety of media common in an equine environment, such as stable bedding, manure, food, and water troughs, and even harnesses and tack. Handling of sources like these can transmit the disease by contact with mucous membranes, contact with cuts or abrasions, or inhalation into the lungs.

Glanders occurs in three clinical forms: acute, chronic, and latent. The acute form of glanders is the most common, with a rapid onset, severe signs and symptoms, and a rapid progression usually resulting in death (without treatment). Chronic glanders is less fatal and has less severe signs and symptoms with intermittent recurrences. Latent glanders is the least documented clinical form because of its similarity to chronic glanders, but with a lengthy incubation period. In addition to different clinical forms, there are several different types of infections. The definition of each type of infection varies from source to source. Most commonly documented types of infection are localized infection, nasal mucosa infection (which is a subform of a localized infection), lung infection, and blood infection (bacteremia). Neither the clinical form nor the type of infection are exclusive. One form can potentially cause another, and one infection can lead to another type of infection.

Human-to-human transmission can occur by physical contact with contaminated fluids or materials, but generally has not been observed from aerosol respiration. For example, Robins reported that a whole family became infected because they were near each

664 The information in this section is summarized from 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), 121–146.

other.[665] Similarly, nurses, doctors, and scientist have become infected from being close to infected individuals and matter. Robins reports that as many as 10% of 156 chronic infections he reviewed are from human-to-human contact.[666] *MABW* also comments on the rarity of human-to-human transmission.[667] Thus, glanders is modeled as noncontagious in *AMedP-7.5*.

Assumptions (*AMedP-7.5 Section 5.2.3.2*)

> **Assumption**: Human response to *B. mallei* is independent of the route of exposure.

Although this is likely not true, it was necessary to use this assumption to use the data that were available—most of which are not from aerosol/inhalation exposure—to develop a glanders models.

> **Assumption**: Untreated survivors are unable to RTD because of chronic glanders.

Based on literature review, there is little reason to expect the disease to be eliminated without the use of antibiotics. Survivors would therefore have chronic glanders.

> **Assumption**: When $Flag_{MT}$ = Yes, WIAs begin receiving treatment on the first day they are declared WIA.

There are essentially no data on which to base a treatment model, so it did not make sense to have a complicated model involving many different cohorts with many different times to RTD when there is little confidence in the model. This is a simplifying assumption.

Human Response Model (*AMedP-7.5 Tables 5-28 and 5-29*)

Literature Summary

Table 166 lists the supporting literature we used to develop some of the submodels described below.

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665 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, No. 1, Studies from the Royal Victoria Hospital Montreal (Montreal: Montreal Guertin Printing Co., 1906), 19.

666 Ibid, 38.

667 Gregory and Waag, "Glanders," 126.

Table 166. Glanders Supporting Literature

Year	Author(s)	Number of Cases
1831	John Elliotson	9
1833	John Elliotson	1
1843	Clement Hamerton	3
1854	W. I. Cox	1
1856	Frederick Mason	1
1904	Clark Stewart	3
1906	George Dougall Robins	152
1907	James Taft Pilcher	2
1908	William Hunting	22
1909	Julius M. Bernstein & E. Rock Carling	6
1933	I. Sobol	1
1936	J. F. Burgess	1
1938	A. A. Herold & C. B. Erickson	1
1947	Calderon Howe & Winston R. Miller	6
2001	A. Srinivasan et al.	1

Note: See Appendix B for full reference citations.

Infectivity

Since glanders has been largely eliminated from the modern world, there is little or no human data available from which to develop an infectivity model. Available literature contains very few data on dose response, and no infectivity values can be calculated directly from case reports. We were also unable to find any infectivity data for nonhuman primates and other large animal models. The only available data are from small animals like rats, mice, and hamsters. This dearth of data makes an estimate of an infective dose difficult to develop.

MABW regards glanders (particularly aerosolized glanders) as highly infectious,[668] but does not attach a specific number of organisms to the statement. The belief seems to be based on the incidence of laboratory infections that presumably resulted from exposure to an aerosol. The authors of the *P-8 BMR* used data from Howe and Miller[669] to estimate the ID_{50}. Specifically, those data are that 4 accidental human infections occurred as a result of exposure to a strain with an ID_{50} of 20 to 30 organisms in hamsters. Two other cases were from a strain with an ID_{50} of five organisms in hamsters. After first deciding that the probit

668 Gregory and Waag, "Glanders," 135.

669 Calderon Howe and Winston R. Miller, "Human Glanders: Report of Six Cases," *Annals of Internal Medicine* 26, No. 1 (1947): 93–115

slope they used for *F. tularensis* should be used for glanders,[670] the authors of the *P-8 BMR* set the ID_{10} equal to 5.3 organisms and the ID_{50} equal to 24.5 organisms—presumably by arbitrarily adjusting the ID_{50} to make the probit curve approximately line up with the hamster data (although that is not explicitly stated).

Even though we are aware of the many problems with this model—equating humans with guinea pigs chief among them—we have used it in *AMedP-7.5* because it has been the accepted model for some time and we have no particular data that could be used to generate an alternate model. Creating a new model that is equally unsupported by relevant data would only make the situation worse.

Lethality

MABW states, "the majority of human glanders cases occurred before antibiotics, and over 90% of these people died."[671] The *P-8 BMR* assumes 100% lethality.[672]

In contrast, the data we pulled for untreated glanders patients from the reports listed in Table 166 were the following: of 152 patients, 105 died, or 69.08%. Cases in which the final outcome could not be determined clearly from the literature were not included. For *AMedP-7.5* the percentage was rounded to 70%. This value is consistent with statements of high lethality, but does somewhat contradict *MABW*.

Incubation Period

The *P-8 BMR* models the glanders incubation period as widely varying, with an average time of 10 to 14 days, but as little as 4 days for high doses and as much as a few weeks for low doses.[673] *MABW* describes the incubation period as ranging from less than a day to several weeks[674] and differentiates between cutaneous and mucous infection (as short as 3 to 5 days) and an inhalational infection (2 to 3 weeks).[675]

From the reports in Table 166, there were only incubation period data for 37 cases. Even though different routes of exposure incubate at different rates, most documented incubation periods are from cutaneous exposures or accidental inoculations. Since there are a limited number of case reports that include incubation periods, all but three data points were used regardless of their route of exposure or clinical form. Two cases were extreme

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670 The reasoning given is "due to their similarities (bacterial)." Thus, it seems that the only basis for using the *F. tularensis* probit slope is that both agents are bacterial. See Anno et al., *AMedP-8* (*Biological*) *Methods Report*, 211. We do note that since most infectious agents have slopes in the range of 1–4 probits/log (dose), the value from *F. tularensis* is probably not far off.

671 Gregory and Waag, "Glanders," 140.

672 Anno et al., *AMedP-8* (*Biological*) *Methods Report*, 49.

673 Anno et al., *AMedP-8* (*Biological*) *Methods Report*, 212.

674 Gregory and Waag, "Glanders," 128.

675 Gregory and Waag, "Glanders," 131.

outliers and the third case was too ambiguous to use. From the remaining 34 data points, we estimated a mean incubation period of 8 days (7.82 days). Table 167 represents the 37 cases that were used to determine the incubation period. After examining the data, there was an additional case that is an outlier, but not as extreme as the other. If this value is excluded the mean incubation period becomes 7 days (6.79 days), consistent with *MABW*. Using the @RISK software,[676] a lognormal function was fit to the data in Table 167; the fitted distribution has a mean of 8.29 days and a standard deviation of 13.0 days.

Table 167. Documented Glanders Incubation Periods

Source	Incubation Period	Rounded Incubation Period (days)	Note
Elliotson 1830	3 days	3	
———	6 weeks	42	Latent
Cox 1854	24 hours	1	
Stewart1904	6 days	6	
Robins1906	local 6 hours – 4 days	1	
———	10+ years?	3650	Outlier
———	7 days	7	
———	4 days	4	
———	12 days	12	
———	7 days	7	
———	a few days	3	
———	under 3 weeks	2	
———	48 hours	2	
———	24 hours	1	
———	15 days	15	
———	7 days	7	
———	8 days	8	
———	a few hours	1	
———	48 hours	2	
———	24 hours?	1	
———	several months	121.7	Outlier
———	1 day	1	
———	less than 21 days	20	
———	1 week	7	

676 *@Risk for Excel.*

Source	Incubation Period	Rounded Incubation Period (days)	Note
———	a few hours	1	
Herold1938	7 days	7	
Srinivasan 2001	a few days – several weeks		Too broad
Pilcher1907	25 days	25	
———	5 days	5	
Bernstein1909	9 days	9	
Sobol 1933	a few days	3	
Howe1946	12 days	12	
———	less than 1 day	1	
Hunting1908	~9 days	9	
———	~7 days	7	
———	7 days	7	
———	15 days	15	

Note: See Appendix B for full reference citations.

Injury Profile

Both *MABW* and the *P-8 BMR* contain varying descriptions of the common symptoms experienced from a glanders infection. The *P-8 BMR* lists the most common symptoms, consisting of abscesses, fever, nasal involvement, pain, skin eruptions, cough, bronchitis, asthenia, oral and pharynx involvement, rigors, emaciation, delirium, ocular involvement, gastrointestinal symptoms, sweating, and insomnia.[677] *MABW* describes the generalized symptoms as consisting of fever, myalgia, headache, fatigue, diarrhea, weight loss, and lymphangitis.[678]

The case reports were reviewed to create a list of common signs and symptoms. Each was counted to see how often each symptom occurred out of all the cases to build a common symptom list. Because symptoms vary so greatly between individuals, even symptoms with relatively infrequent incidence were considered. Nineteen symptoms (every symptom listed in Table 168) appeared in at least 10% of patients, 9 symptoms appeared in at least 20% of patients, and only 3 symptoms appeared in more than 30% of patients.

677 Anno et al., *AMedP-8 (Biological) Methods Report*, 256.

678 Gregory and Waag, “Glanders,” 122.

Table 168. Glanders Symptoms Occurring in over 10% of Cases

Symptom	Incidence
Abscesses	57.74%
Swelling	31.55%
Nasal discharge	30.36%
Localized pain and inflammation	29.76%
Pain	28.57%
Ulcerations	27.38%
Chills	26.19%
Phlegmon	25.60%
Pustules	22.02%
Fever	19.64%
Suppuration	19.64%
Cough	16.67%
Red streaks	13.69%
Necrosis	12.50%
Diarrhea	11.90%
Emaciation	10.71%
Papular eruption	10.71%
Delirium	10.12%
Dyspnea (difficulty breathing)	10.12%

The *P-8 BMR* authors estimated when each symptom would occur during the illness; they assumed 100% lethality, so only one Injury Profile was created. The Injury Profile starts on the first day the first symptom starts. In their model the first symptoms are mild, consisting of fever, malaise, loss of appetite, nausea, and headache. Moderate symptoms, which arise 6 days later, consist of painful nodules and swellings on face and limbs in addition to previously stated symptoms. Two weeks into the duration of the illness, additional symptoms arise; there are pustular eruptions on most of body, nasal mucosa becomes reddened and edematous with ulceration and purulent discharge, and dyspnea may be present. Around the 17th day the most severe symptoms arise, consisting of respiratory problems, muscular abscesses, metastatic pneumonia, diarrhea, severe pyemia with suppurating pustules covering body, and emaciation ending terminally.[679]

MABW describes several symptom sets according to the originating manifestation. Focusing mainly on an aerosolized glanders attack, glanders would primarily cause nasal or ocular infections and possibly pulmonary infections. The nasal or ocular mucosa

679 Anno et al., *AMedP-8 (Biological) Methods Report*, 50.

infection would produce a localized infection. The infected mucosa would swell and excrete a mucopurulent discharge. Papular and ulcerative lesions may appear with blisters and sores. The nose may swell and become inflamed with copious discharge. Facial swelling is possible, along with the infection spreading to the nasal septum and the bony tissue causing fistulae and tissue destruction. Lymph glands may also become inflamed and suppurate. Dissemination would spread the infection further into the body, infecting the respiratory tract and lungs (pulmonary infection). Pulmonary infections would cause tracheitis and bronchitis with cough and mucopurulent sputum production. Other symptoms that can arise include fever, headache, fatigue, prostration, pneumonia, pulmonary abscess, pleuritis, pleural effusion, cough, dyspnea, chest pain, and mucopurulent sputum.[680]

Two Injury Profiles were created from the data collected, one for survivors and the other for non-survivors, using the information extracted from the reviewed case reports, *MABW*, and the *P-8 BMR*. Since glanders can infect by several routes of exposure, there is, in reality, no "standard" symptom set. Symptoms that were experienced in more than 10% of individuals were used to create a "general" Injury Profile for the model. After the onset of infection, the modeled symptoms are localized pain and inflammation, fever, swelling, chills, and phlegmon (Stage 1, Injury Severity Level 1). Stage 2 involves moderate (Injury Severity Level 2) symptoms consisting of cough, suppuration, red streaks, papular eruption nasal discharge, abscess, pain, and ulcerations. Stage 3 is characterized by severe (Injury Severity Level 3) symptoms consisting of diarrhea, emaciation, pustules, necrosis, dyspnea, and delirium. The non-surviving cohort dies at the end of Stage 3. Stage 4 for the surviving cohort is characterized as the chronic form of glanders, with protracted periods of no symptoms, interrupted by periods of illness that could be similar to Stage 2 or Stage 3. Since the majority of the chronic period would be associated with no symptoms, the assigned severity is Mild. Anyone with chronic glanders cannot RTD. The Injury Profile is summarized in Table 169

Table 169. Glanders Injury Profile

	Stage 1	Stage 2	Stage 3	Stage 4 (survivors)
Signs and symptoms (S/S)	Localized pain and inflammation, fever, swelling, chills, and phlegmon	Cough, suppuration, red streaks, papular eruption nasal discharge,	Diarrhea, emaciation, pustules, necrosis, dyspnea, and delirium	Chronic glanders

680 Gregory and Waag, "Glanders," 131.

		abscess, pain, and ulcerations		
S/S Severity	1 (Mild)	2 (Moderate)	3 (Severe)	1 (Mild)

Duration of Illness

MABW estimates the duration of illness to range from a few days to weeks or months or years.[681] The *P-8 BMR* estimates that the acute form lasts 10 to 30 days, with an average of 19 days, and that chronic glanders lasts months to years.[682]

These durations were compared to all case reports listed in Table 166 regardless of clinical forms, excluding cases that were incompletely synopsized. We used 174 cases to estimate the overall duration of illness, generating a value of 370 days. This value is significantly longer than previous estimates because different clinical forms were not distinguished—chronic and latent glanders were included. Robins suggests that although there is in reality no clear point at which the distinction between the acute and chronic or latent forms can be made, 6 weeks is a useful maximum to define the acute cases.[683]

The data points that matched this criterion are shown in Table 170, along with the total cumulative fraction of cases as of each of the days corresponding to the data. Using the @RISK software[684] tool to fit a distribution to the first and third columns of Table 170, we found that a Weibull distribution with a mean duration of 23.1 days, standard deviation of 12.7 days, a shape parameter of 1.90 (unitless), and a scale parameter of 26.0 days created the best fit according to the root-mean-square error.

Table 170. Data Points Used to Generate Glanders Overall Duration of Illness Model

Length (days)	# Cases	Total Cumulative Fraction of Cases
5	1	1/36 = 2.78%
8	1	2/36 = 5.56%
9	2	4/36 = 11.11%
11	2	6/36 = 16.67%
13	1	7/36 = 19.44%
14	4	11/36 = 30.56%
15	1	12/36 = 33.33%
16	1	13/36 = 36.11%
17	3	16/36 = 44.44%
21	1	17/36 = 47.22%

681 Gregory and Waag, “Glanders,” 130.

682 Anno et al., *AMedP-8* (*Biological*) *Methods Report*, 213.

683 Robins, *A Study of Chronic Glanders in Man*, iv.

684 *@Risk for Excel*.

Length (days)	# Cases	Total Cumulative Fraction of Cases
22	1	18/36 = 50.00%
24	1	19/36 = 52.78%
25	2	21/36 = 58.33%
27	1	22/36 = 61.11%
28	3	25/36 = 69.44%
30	1	26/36 = 72.22%
42	10	36/36 = 100.00%

We were unable to estimate which fraction of the total duration corresponds to each of the three stages[685] from the the reports cited in Table 166. However, the *P-8 BMR* has a 4 severity model based on analysis of 10 cases.[686] Equating its severity 1 with Stage 1, its severity 2 with Stage 2, and its severities 3 and 4 with Stage 3, the durations can be broken down as 30%, 45%, and 25% of the total duration of illness, respectively. We calculated the means and standard deviations of the three stages accordingly.

For patients who do not receive antibiotics, the model includes an indefinite period of chronic glanders.

Medical Countermeasures and Treatment Model

Lethality

MABW notes that although previous reports have estimated higher CFRs, the eight patients treated for laboratory-acquired glanders all survived, and that the reason for higher estimates may be because they are from an era when effective antibiotics for glanders had not yet been discovered.[687] Since there are no other cases in the literature describing modern medical treatment for glanders patients, we used the suggestion by *MABW*—a 0% CFR for treated glanders.

a. *Injury Profile*

With antibiotic treatment, glanders survivors are not expected to have chronic glanders, so there is no Stage 4 for treated survivors. Although there is no citable information to justify other changes to the Injury Profile, it does not make sense for a person receiving antibiotic care to continue to worsen to a significant degree; on the contrary, one expects their symptoms to improve. Thus, Stage 3 for treated personnel is changed to Injury Severity Level 1. Implementing this is problematic since if the casualty criterion is WIA(3^+), a person would become WIA (as an untreated person) by entering

685 No estimate of duration is needed for the fourth stage because it represents chronic glanders.

686 Anno et al., *AMedP-8* (*Biological*) *Methods Report*, 50–52.

687 Gregory and Waag, “Glanders,” 134.

Stage 3, but would then immediately be "downgraded" to Injury Severity Level 1. Although this is an odd way to implement the model, we find it more palatable than modeling a person receiving antibiotic treatment as progressing to worse symptoms. The final Injury Profiles are shown in Section 0.

b. Duration of Illness

This model is loosely based on the eight patients treated for laboratory-acquired glanders, as summarized in *MABW*.[688] Stage 1 for treated patients is 7 days; Stage 2 for treated patients is ICU care for 14 days, and release from the ICU is followed by a 70-day recovery and eventual RTD (Stage 3).

Model Summary

Table 171 through Table 173 summarize the model parameters for glanders used in *AMedP-7.5*. While the parameters in these tables represent current best estimates, any new data that become available, particularly for inhalational exposure in nonhuman primates or in humans, would improve the model.

Table 171. Glanders Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 24.5 organisms Probit slope = 1.93 probits/log (dose)
Lethality (untreated)	Rate	70%
Lethality (treated)	Rate	0%
Incubation period	Lognormal distribution	Mean = 8.29 days Standard deviation = 13.0 days μ = 1.495; σ = 1.114
Duration of illness		
• Stage 1 (untreated)	Weibull distribution	Mean = 6.9 days Standard deviation = 3.8 days α = 1.9, β = 7.8 days
• Stage 2 (untreated)	Weibull distribution	Mean = 10.4 days Standard deviation = 5.7 days α = 1.9, β = 11.7 days
• Stage 3 (untreated)	Weibull distribution	Mean = 5.8 days Standard deviation = 3.2 days α = 1.9, β = 6.5 days
• Stage 4 (untreated)	Constant	indefinite
• Stage 1 (treated)	Constant	7 days
• Stage 2 (treated)	Constant	14 days
• Stage 3 (treated)	Constant	70 days

688 Gregory and Waag, "Glanders," 132–133.

Table 172. Glanders Untreated Injury Profile

	Stage 1	Stage 2	Stage 3	Stage 4 (survivors)
Signs and symptoms (S/S)	Localized pain and inflammation, fever, swelling, chills, and phlegmon	Cough, suppuration, red streaks, papular eruption nasal discharge, abscess, pain, and ulcerations	Diarrhea, emaciation, pustules, necrosis, dyspnea, and delirium	Chronic glanders
S/S Severity	1 (Mild)	2 (Moderate)	3 (Severe)	1 (Mild)

Table 173. Glanders Treated Injury Profile

	Stage 1	Stage 2	Stage 3
Signs and symptoms (S/S)	Localized pain and inflammation, fever, swelling, chills, and phlegmon	Cough, suppuration, red streaks, papular eruption nasal discharge, abscess, pain, and ulcerations	Resolution of fever and gradual clearing of infection
S/S Severity	1 (Mild)	2 (Moderate)	3 (Severe)

Cohorts and Special Considerations (*AMedP-7.5 Section 5.2.3.3*)

The definitions and calculations of the populations of cohorts are straightforward and need no further explanation.

1.22. Melioidosis Model
(*AMedP-7.5 Section 5.2.4*)

Introduction

B. pseudomallei, the causative agent of melioidosis, is a gram-negative bacterium. The bacterium is quite robust and can survive in distilled water for years. Stanton and Fletcher, who isolated the bacterium from an outbreak of a septicemic disease in a guinea pig colony in Kuala Lumpur, coined the term "melioidosis" (meaning "glanders-like illness" in Greek) in 1921.[689] There are many strains of *B. pseudomallei*, ranging in virulence from the relatively benign to the highly virulent (some 27 genomes identified to date).[690] In human case data, the strain is generally not known, so we derived the submodel parameters without consideration of the strain. We report the strain used in the animal experiments that support the infectivity model but did not attempt to account for differences in virulence between the strains.

Melioidosis is endemic in Southeast Asia and Northern Australia, where the bacteria reside in soils and in pooled surface water such as rice paddies and irrigation ditches. The disease occurs frequently in most other countries of Southeast Asia and sporadically in many other countries.[691] Routes of natural infection include percutaneous, inhalation, ingestion, and aspiration,[692] and the route of exposure *does* affect the presentation of disease.[693] Because of the high incidence of persons working in agriculture who contract melioidosis and the prevalence of the bacterium in soils in endemic locales, percutaneous inoculation is considered the primary natural route of infection. Inhalation and aspiration of contaminated water (liquid or aerosol) are also common routes of exposure, however, as demonstrated by the relatively high incidence of the disease in helicopter crews in

689 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), 148.

690 Joseph J. Gillespie et al., "Patric: The Comprehensive Bacterial Bioinformatics Resource with a Focus on Human Pathogenic Species," *Infection and Immunity* 79, no. 11 (2011): 4286–4298.

691 Direk Limmathurotsakul and Sharon J. Peacock, "Melioidosis: A Clinical Overview," *British Medical Bulletin* 99, no. 1 (2011): 125–139; Allen C. Cheng and Bart J. Currie, "Melioidosis: Epidemiology, Pathophysiology, and Management," *Clinical Microbiology Reviews* 18, no. 2 (2005): 383–416.

692 Cheng and Currie, "Melioidosis: Epidemiology, Pathophysiology, and Management"; Wirongrong Chierakul et al., "Melioidosis in 6 Tsunami Survivors in Southern Thailand," *Clinical Infectious Diseases* 41, no. 7 (2005): 982–990.

693 W. Joost Wiersinga, Bart J. Currie, and Sharon J. Peacock, "Melioidosis," *New England Journal of Medicine* 367, no. 11 (2012): 1035–1044, 1040, Figure 3.

Vietnam,[694] the increased occurrence of infections in endemic areas during seasons of heavy rains and winds,[695] and clusters of cases occurring after tsunamis[696] and typhoons.[697] Incidents of person-to-person transmission have been recorded, although they are rare. At least one case of nosocomial transmission has also been reported,[698] but we modeled melioidosis as a noncontagious disease.

Melioidosis in humans can be chronic or acute. The acute version presents in several different ways, including localized soft tissue infections, acute pulmonary infections, and acute fulminant septicemia. The common theme of all these presentations is the presence of abscesses in the affected organs. The chronic variant of melioidosis often presents with chronic localized infections. High mortality rates result primarily from the acute version. With the chronic version, symptoms can appear sporadically for a number of years—perhaps a lifetime.[699] Acute pulmonary infections (pneumonia) represent the most common presentation, occurring in about half of human cases.[700] Inhalation of *B. pseudomallei* can lead to the acute pulmonary and septicemic forms of the disease but not the local form. However, it is also possible for a percutaneous or ingestion inoculation to lead to bacteremia and subsequent pulmonary symptoms.[701]

Timely diagnosis of melioidosis has proven difficult, especially when the disease occurs unexpectedly. It can take 2 to 3 days to obtain definitive test results, by which time the patient could be in serious condition or even dead.[702] To be effective, treatment with the correct course of antibiotics must begin immediately and continue for several weeks or more. Thus, in endemic locations, common practice is to begin antibiotic therapy immediately upon suspicion of the disease.

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694 Spurgeon Neel, *Medical Support of the U.S. Army in Vietnam, 1965–1970*, Vietnam Studies (Washington, DC: Department of the Army, 1991).

695 Bart J. Currie, Linda Ward, and Allen C. Cheng, "The Epidemiology and Clinical Spectrum of Melioidosis: 540 Cases from the 20 Year Darwin Prospective Study," *PLoS Neglected Tropical Diseases* 4, no. 11 (2010): e900, 2.

696 Chierakul et al., "Melioidosis in 6 Tsunami Survivors."

697 Wen-Chien Ko et al., "Melioidosis Outbreak after Typhoon, Southern Taiwan," *Emerging Infectious Diseases* 13, no. 6 (2007): 896–898.

698 Cheng and Currie, "Melioidosis: Epidemiology, Pathophysiology, and Management," 398.

699 In 2005, symptoms appeared 62 years after presumed exposure in a World War II veteran who was a Japanese prisoner of war. See Limmathurotsakul and Peacock, "Melioidosis: A Clinical Overview," 129.

700 Currie, Ward, and Cheng, "The Epidemiology and Clinical Spectrum of Melioidosis," 8.

701 Wiersinga, Currie, and Peacock, "Melioidosis," 1040 (Figure 3).

702 Timothy J. J. Inglis, Dionne B. Rolim, and Jorge L. N. Rodriguez, "Clinical Guideline for Diagnosis and Management of Melioidosis," *Revista do Instituto de Medicina Tropical de São Paolo* 48, no. 1 (2006): 1–4.

Assumption and Limitations (*AMedP-7.5 Section 5.2.4.2*)

Assumption: The population does not have melioidosis risk factors.

Supporting reasoning was given in the Introduction, Section 0.

Limitation: The methodology only accounts for acute onset melioidosis with pulmonary presentation.

Supporting reasoning was given in the Introduction, Section 0.

Limitation: Although the model requires the user to specify a day on which antibiotic treatment becomes available ($d_{trt\text{-}meli}$), it does *not* apply treatment to every person on that day; only those who have been declared WIA are modeled to begin receiving antibiotics on that day. Those who are declared WIA after $d_{trt\text{-}meli}$ are modeled to begin receiving antibiotics on the day they are declared WIA.

Although this is stated as a limitation, it is actually the most sensible way to apply treatment.

Human Response Model (*AMedP-7.5 Tables 5-40 and 5-41*)

Applicability of Data Sources

Because the models are intended to represent the disease that would be caused by a biological weapon in patients who receive no medical treatment (with later modification to incorporate the effects of medical treatment), we filtered the total dataset where possible to remove data that are not relevant.

Practically all case reports and epidemiological surveys report on patients who received medical treatment. We located one brief report on U.S. military forces who did not receive medical treatment because the disease was not recognized,[703] but the only usable information provided is the CFR. We used these data for the lethality model. For the other submodels, such data were not available. The infectivity and incubation period models are unaffected since medical treatment does not occur until after the onset of disease, but administration of antibiotics almost certainly affects the duration of illness and severity of disease (Injury Profile).

Perhaps the most important factor to consider is the presence or absence of risk factors in the patients. In the "Darwin Study"[704] of 540 cases of melioidosis over 20 years, the authors found that the only predictor of mortality was "the presence of defined risk factors

703 Neel, *Medical Support*, 44–45.

704 So named because of the hospital (Royal Darwin Hospital, Australia) in which the study took place.

such as diabetes, hazardous alcohol use, chronic lung or renal disease and older age."[705] While it is easy to dismiss most of these risk factors as not applicable to the median active military person, hazardous alcohol use deserves some consideration. The definition of "hazardous alcohol use" is important. The authors of the study go on to state that their clinical impression is that the risk is associated mainly with binge drinking and with high blood alcohol levels at the time of exposure. Results from a survey of U.S. active duty military personnel (ADMP) revealed that although 43.2% of ADMP reported binge drinking in the previous month, only 20% of ADMP were responsible for 71.5% of binge-drinking episodes.[706] Combined with the association of risk with high blood alcohol levels *at the time of exposure* (i.e., while on duty, possibly in a combat situation), we do not believe that this risk factor should be applied to the *median* active military person.

Another factor is the route of exposure. The previous section indicated that any route of exposure *can* lead to pulmonary symptoms but that inhalation (and therefore likely aspiration) is *expected* to lead to pulmonary symptoms. Thus, when the route of exposure is known, inhalation and aspiration data are preferred. When the route of exposure is not known (often the case), we deemed the data to be relevant only if the patient had pulmonary symptoms. Thus, we did not consider cases presenting with only local abscesses. This point is important since these cases appear to have a 0% mortality rate, which significantly decreases the overall CFR when all cases are considered together.

Further, the 20-year report of the Darwin Study states that of their 106 patients with no risk factors, only 6 had septic shock (a result of septicemia).[707] Including all 540 cases, 50% of those with septic shock (n = 116) died despite medical treatment, whereas only 4% of those without septic shock (n = 424) died.[708] All patients were provided medical treatment, so the exact numbers do not apply to the untreated model, but the more relevant issue is the importance of septic shock. We assumed that septic shock in the absence of medical treatment leads invariably to death and that casualties who do not experience septic shock will survive.

Combining the various issues led to the following requirements for data that we used in parameterizing the submodels. The first requirement obviously only applies for the untreated model.

- The patient must not have received medical treatment, particularly antibiotics.

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705 Currie, Ward, and Cheng, "The Epidemiology and Clinical Spectrum of Melioidosis," 10.

706 Mandy A. Stahre et al., "Binge Drinking Among U.S. Active-Duty Military Personnel," *American Journal of Preventive Medicine* 36, no. 3 (2009): 208.

707 Currie, Ward, and Cheng, "The Epidemiology and Clinical Spectrum of Melioidosis," 4.

708 Ibid., 3 (Table 2).

- The patient must not have any known risk factors.
- The patient must have pulmonary symptoms.
  - For survivors, the symptoms must not include septic shock.
  - For nonsurvivors, the symptoms must include septic shock.
- If the route of exposure is known, it must be either inhalation or aspiration.

These requirements rendered a large fraction of the data in the literature unavailable for the model development. Where necessary to enable development of the models, these requirements were relaxed. Relaxation of the rules is noted in the text of this chapter.

Literature Summary

Human Data

The two references listed in Section 0 were useful for a general understanding of melioidosis. Specific data from naturally occurring infections in humans are plentiful in the literature. As discussed previously, the bigger issue with melioidosis is identifying cases that are applicable for the models. To use the available human data, we were forced to relax some of the restrictions specified previously. This situation is not ideal and means that there is additional uncertainty in the models. However, we deemed that approach better than attempting to use animal data. The specific sources of human data are cited throughout the chapter, as appropriate.

The only available data on laboratory-acquired melioidosis infections come from two case studies of confirmed laboratory infections.[709] Details of the cases are discussed as warranted in the subsequent sections. Other cases likely have occurred but no specific, detailed information is available.[710]

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709 Robert N. Green and Peter G. Tuffnell, "Laboratory Acquired Melioidosis," *American Journal of Medicine* 44, no. 4 (1968): 599–605; Walter F. Schlech et al., "Laboratory-Acquired Infection with *Pseudomonas pseudomallei* (Melioidosis)," *New England Journal of Medicine* 305, no. 19 (1981): 1133–1135.

710 The Public Health Service of Canada website contains a "Materials Safety Data Sheet" on melioidosis (see Public Health Agency of Canada (PHAC) Website, "*Burkholderia* (*Pseudomonas*) *pseudomallei* – Material Safety Data Sheets (MSDS)," last modified February 18, 2011, http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/msds26e-eng.php), which states the following: "Laboratory-acquired infections: 20 cases of infection, with 7 deaths, reported up to 1976; one case associated with massive aerosol and skin contact exposure; an additional infection resulted from an aerosol created during open-flask sonication of a culture presumed to be *P. cepacia*; 3 laboratory workers were reported to have subclinical infections in 1992." No references are provided. The two specific cases mentioned are the same two described in this chapter.

Animal Data

Because we found a sufficient amount of human data for the other submodels, we only used animal data to derive the infectivity model. The data supporting the infectivity model, from experiments in which NHPs were exposed to aerosols of *B. pseudomallei*, allowed for estimation of the ID_{50} and the probit slope.

Further, it is not clear that there are any "good" animal models in terms of incubation, duration, and severity, even though animal models do mimic some aspects of the human disease (such as immune response).[711]

Infectivity

The animal data show that the bacterial strain and route of exposure significantly affect the likelihood of illness,[712] so this submodel is not constrained by the fact that indigenous populations in endemic regions have a relatively high prevalence of antibodies to *B. pseudomallei*.[713] The indigenous populations may have been exposed to a low dose, to a low virulence strain, or via a route for which the ID_{50} is significantly higher than the inhalation ID_{50}. Thus, the high incidence of antibodies does not necessarily mean that the infectious dose is very high. In any case, we found no human data that could be used to develop an infectivity model.

There is a vast amount of literature on studies with small animals, but as stated in a recent review, "There is no good evidence to indicate whether hamsters, mice, or diabetic rats challenged with *B. pseudomallei* are the best models of melioidosis in humans."[714] Because data from inhalation experiments with NHPs supported the estimation of an ID_{50} and a probit slope, we did not consider other animal data.

In 2011, Nelson et al. reported research in which they challenged marmosets with aerosols of *B. pseudomallei* strain K96243.[715] For each dose level, they used only one marmoset. Male marmosets inhaled doses of 2, 25, 180, and 2600 CFU, and female

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711 Richard W. Titball et al., "*Burkholderia pseudomallei*: Animal Models of Infection," *Transactions of the Royal Society of Tropical Medicine and Hygiene* 102, Supp. 1 (2008): S111–S116; Erin van Schaik et al., "Development of Novel Animal Infection Models for the Study of Acute and Chronic *Burkholderia pseudomallei* Pulmonary Infections," *Microbes and Infection* 10, nos. 12–13 (2008): 1291–1299; Jonathan Mark Warawa, "Evaluation of Surrogate Animal Models of Melioidosis," *Frontiers in Microbiology* 1, Article 141 (2010): 1–12.

712 van Schaik et al., "Development of Novel Animal Infection Models," Warawa, "Evaluation of Surrogate Animal Models."

713 Timothy J. J. Inglis and Jose-Luis Sagripanti, *Environmental Survival, Military Relevance, and Persistence of Burkholderia pseudomallei*, ECBC-TR-507 (APG: ECBC, April 2007), 13.

714 Titball et al., "*Burkholderia pseudomallei:* Animal Models," S113.

715 Michelle Nelson et al., "Development of an Acute Model of Inhalational Melioidosis in the Common Marmoset (*Callithrix Jacchus*)," *International Journal of Experimental Pathology* 92, no. 6 (2011): 428–435.

marmosets inhaled doses of 5, 63, 150, and 7700 CFU. Every marmoset became ill and was subsequently euthanized upon exhibiting severe clinical signs of illness. These data are consistent with the other NHP data and the proposed model, but we did not use them because marmosets are relatively primitive and therefore less similar to humans than higher primates for which we have a fuller dataset.

The other NHP data of which we are aware is from work by Yeager et al. at USAMRIID. The publicly available record of their work is published in a peer-reviewed journal article.[716] We also requested and received from Dr. Yeager some additional infectivity data that were not published in the journal article.[717] The information summarized below comes from the journal article and the privately emailed supporting data.

In the study, the investigators challenged 24 RMs and 25 AGMs with aerosols of *B. pseudomallei* strain 1026b. The animals were exposed to doses between 10 and 10^6 CFU. To avoid issues with clearance for public release of data potentially supporting determination of an NHP LD_{50}, we do not include information on which specific doses lead to death or survival.

Based on temperature data, hematology, and pathology, it appears that all 24 RMs became infected. Based on the same types of data, it appears that three AGMs did not become infected.[718] Therefore, we used the AGM data for the infectivity model. Table 174 summarizes the dataset for the AGMs as provided by Dr. Yeager. One issue Dr. Yeager pointed out in his email is that the data are for *presented* dose, not *inhaled* dose. This distinction is important because the infectivity models for *AMedP-7.5* should be based on inhaled dose, and an inhaled dose is some fraction of the presented dose. Thus, an infectivity model derived from presented dose data will overestimate the ID_{50}. The probit slope estimate should not be affected by the use of presented dose. Despite the data being for presented dose, the AGM data are the best data available and so we used them.

Although the data are reported on a single AGM basis, some AGMs were presented with the same dose and had different outcomes, so probit analysis is possible. Specifically, two of three AGMs presented with 15 CFU became ill. Probit analysis including all the

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716 John J. Yeager et al., "Natural History of Inhalation Melioidosis in Rhesus Macaques (*Macaca Mulatta*) and African Green Monkeys (*Chlorocebus Aethiops*)," *Infection and Immunity* 80, no. 9 (2012):
3332–3340.

717 John J. Yeager, "Infectivity Data on Inhalation Melioidosis (*Burkholderia pseudomallei*)," emailed to IDA author Dr. Audrey Kelley on September 12, 2013.

718 AGM #8 did have elevated body temperature and leukocytes after Day 14, but this condition was caused by a secondary infection.

data in Table 174 fails to converge. Removing the four data points with the highest presented dose—1,070,000, 24,800, 4680, and 4030 CFU[719]—results in the analysis converging at an ID_{50} of 15 CFU (no confidence interval available) and a probit slope of 3.5 probits/log (dose) (95% CI 0 to 9.1).

Since the ID_{50} estimate from probit analysis is equal to the lowest dose in the AGM dataset and since those data are for the presented dose instead of the inhaled dose, we have very little confidence in the specific ID_{50} value estimated here. However, regardless of the specific value, the AGM data, supported by the RM data (which show that 5 of 5 RMs with doses less than 40 CFU became ill) indicate that the value is *very low*. In that sense, we are confident that the model—an ID_{50} of 15 CFU and a probit slope of 3.5 probits/log (dose)—will give reasonable estimates of the number of individuals who will become ill following an aerosol challenge with *B. pseudomallei*.

Table 174. Infectivity Data for Inhalation of *B. pseudomallei* in AGMs

AGM #	Presented Dose (CFU)	NHP Became Ill?	AGM #	Presented Dose (CFU)	NHP Became Ill?
1	1,070,000	Yes	14	110	Yes
2	24,800	Yes	15	121	Yes
3	107	Yes	16	2,680	Yes
4	15	Yes	17	4,680	Yes
5	51	Yes	18	3,570	Yes
6	16	Yes	19	2,190	Yes
7	15	Yes	20	2,660	Yes
8	17	No	21	3,500	Yes
9	17	No	22	3,850	Yes
10	15	No	23	4,030	Yes
11	112	Yes	24	2,560	Yes
12	95	Yes	25	2,660	Yes
13	108	Yes			

719 We also tested the effect of removing other data points since this approach is somewhat arbitrary. Removing any other data point with dose > 1000 CFU only affects the confidence intervals. Removing data points with dose < 1000 CFU affect the ID_{50} and probit slope. We only removed data points as necessary to get the iteration to converge.

Lethality

Many reports on animal experiments state an LD_{50},[720] which implies that the lethality of melioidosis is dose dependent. However, because most authors did not discuss illness separately from lethality (e.g., by noting how many animals became ill separately from how many died), it is possible that the lethality is near or equal to 100% in animals that receive no medical treatment and that the fidelity of the animal data simply does not allow a distinction between the LD_{50} and the ID_{50}. The report on studies with NHPs did note that 2 of 20 monkeys survived,[721] but it is not certain that their survival was a function of dose rather than simple chance. To be consistent with the other lethality models for replicating organisms and because the concept of dose-dependent lethality in replicating organisms is very unusual, the recommended model is a CFR. The specific recommended CFR is based on historical human data, as discussed below.

The CFR for humans naturally exposed to *B. pseudomallei* varies greatly as a function of route of exposure, presence of risk factors, and the specific presentation of disease. As stated in Subsection 0, the data must be filtered. Specifically, data must be related to patients with pulmonary symptoms and without any known risk factors. Further, for the untreated model, data must be for patients who did not receive antibiotics. Data for patients who did receive antibiotics will be considered in Subsection 0.

Given the limitations on what data are relevant, no single report is relevant. However, one report comes close, and the results from it can be modified to suit the restrictions based on statistics in other reports.

Maj. Gen. Spurgeon Neel, a prominent medical authority during the Vietnam War, published the data in Table 175 and provided the following information for context:

> The unfamiliarity of American physicians with this disease and their concomitant failure to diagnose and treat it properly in all but the most severe cases are shown in the low rate and high fatality incidence in 1966.[722]

720 See for example the following review, which lists around 100 reported LD_{50}s: Warawa, "Evaluation of Surrogate Animal Models."

721 Yeager et al., "Natural History of Inhalation Melioidosis," 3339.

722 Neel, *Medical Support*, 44.

Table 175. Melioidosis Cases in U.S. Troops Deployed to Vietnam

Year	Cases	Deaths	CFR (%)
1965	6	0	0
1966	29	8	28
1967	50	3	6.0
1968	56	1	1.7
1969	46	1	2.1
1970	43	1	2.3

Neel stated that in 1966, only the "most severe" cases were diagnosed and treated.[723] He also indicated that after 1966, American physicians had become more familiar with the disease and began diagnosing and treating it properly,[724] implying that the improved quality of medical treatment was responsible for the lower CFR after 1966. Although the population accurately represents the target population (military personnel) and there was essentially no effective medical treatment in 1966, two issues arose with using the 1966 data as the basis of the untreated lethality model.

The first issue is that the dataset is somewhat small (n = 29). However, no other reports discuss a population without risk factors who did not receive (effective) treatment. One other report is based on a population of soldiers, but the patients were given medical treatment.[725] The only other study that specifically addresses the cohort of patients with no risk factors is the Darwin Study, but the patients in that study also received medical treatment.[726] While it is unfortunate that the dataset is small, there is no remedy.

The second issue is that the distribution of symptoms in the 29 cases is not known. If the majority of the cases were localized abscesses, the CFR would be artificially low, but if the majority were septicemic, the CFR would be artificially high. However, since Neel described the cases as "most severe," we assume that none involved only localized abscesses and that *all* involved pulmonary symptoms and are therefore relevant for

723 Note that because of the unfamiliarity of American physicians with the disease, treatment at that time likely did little to reduce the fatality rate.

724 "Treating it properly" could mean giving antibiotics (instead of none), giving antibiotics earlier in the course of disease, or even giving the *correct* antibiotic.

725 M. K. Lim et al., "*Burkholderia pseudomallei* Infection in the Singapore Armed Forces from 1987 to 1994—an Epidemiological Review," *Annals of the Academy of Medicine Singapore* 26, no. 1 (1997): 13–17.

726 Currie, Ward, and Cheng, "The Epidemiology and Clinical Spectrum of Melioidosis."

estimating the CFR for the untreated model. Thus, the CFR for the untreated lethality model is 28%, the value from the 1966 data in Table 175.

While the supporting data and assumptions leading to this estimate are not ideal, we believe that given the data, it is the best available estimate. Although it is unlikely that new data on cases of untreated melioidosis in a population with no risk factors will ever be published, if new data are published, these data should be used to update the model.

Incubation Period

MABW assigns a very large range to the incubation period: 2 days to many years,[727] although an incubation period of years is rare. Limmathurotsakul and Peacock observed, "The period between *B. pseudomallei* exposure and onset of clinical manifestations is highly variable and often difficult to define."[728] Unfortunately, despite all the incidents of natural infection over the last 50 years or more, the data on incubation period for human exposure are only available in small or insufficient quantities, probably because in most cases, the infected person does not know when he or she was exposed. A few studies provided information about natural infections for patients who knew when they were exposed. Although all the patients described in the reports below were medically treated, medical treatment has no effect on the incubation period, so the data are relevant.

Currie et al. reported the following in one of the early reports from the Darwin Study:

> Of the 206 confirmed cases of melioidosis [in northern Australia], 52 (25%) had likely inoculating events. These were specifically recalled situations where usually percutaneous exposure to soil or muddy water occurred during the monsoon. Despite the presumptive percutaneous inoculation, subsequent disease mostly occurred at distant sites without evidence of active melioidosis at the inoculation site. In the 25 cases where a clear incubation period could be determined between the inoculating injury and the onset of symptoms, the incubation period was 1–21 days (mean 9 days).[729]

There seems to be some uncertainty about the routes of exposure in these cases, but if they were percutaneous as indicated, these data may not accurately reflect the incubation period for aerosol exposure. Therefore, we excluded these data.

One other good, but limited source of incubation data is from the cases of six victims from the 2004 tsunami in Thailand, reported by Chierakul et al.[730] Since the date of the

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727 Vietri and Deshazer, "Melioidosis," 153.

728 Limmathurotsakul and Peacock, "Melioidosis: A Clinical Overview," 129.

729 Bart J. Currie et al., "The Epidemiology of Melioidosis in Australia and Papua New Guinea," *Acta Tropica* 74, nos. 2–3 (2000): 124.

730 Chierakul et al., "Melioidosis in 6 Tsunami Survivors."

tsunami is known with certainty, the incubation period data are of high quality; however, the route of exposure in four of the six cases could have been either percutaneous or aspiration (or both), since four of the six victims experienced both near drowning and laceration, whereas the other two were definitely aspiration. The incubation periods were 3 and 7 days in the clear cases of aspiration exposure, and 3, 6, 10, and 38 days in the cases of uncertain exposure route. Under the assumption that aspiration exposure would result in a shorter incubation period,[731] we used these data points for the analysis, with the exception of the 38-day point that appears to be an outlier (chronic melioidosis, perhaps).

Chierakul et al. also compared the tsunami results to 22 cases of infection by aspiration from near-drowning events that occurred in the endemic area of northeastern Thailand. Unfortunately, the detailed data are not shown, but the following statistics for incubation period are offered: median, 1 day; range, 1–30 days; interquartile range, 1–2 days. Thus, at least half the cases had incubation periods of 1 day or less, and 75% had periods of 2 days or less. All that is apparent about the remaining 25% is that the maximum period was 30 days. Because of lack of more detailed data and to avoid excluding the longer times entirely, we assumed the remaining 25% to be evenly distributed between 2 and 30 days, such that the mean was 16 days (see Table 176).

Table 176. Data Used to Develop Melioidosis Incubation Period Model

Source	Incubation Period (Days)	Weight
Green and Tuffnell	3	1
Schlech et al.	4	1
Chierakul et al.	3	1
———	3	1
———	7	1
———	6	1
———	10	1
———	1	11
———	2	6
———	16	5

Note: See Appendix B for full reference citations.

731 Thus, even if they were exposed by aspiration and laceration, the onset of disease is likely more a function of the aspiration exposure.

Ko et al. reported on an outbreak after a typhoon in Southern Taiwan but only stated that the earliest onset of symptoms was 4 days after the arrival of the typhoon.[732] It could be presumed that the typhoon related cases are from inhalation exposure, but this presumption is not certain. Thus, we did not include the data from the typhoon.

The two cases that were most likely aerosol exposure are those from laboratory exposures in which the incubation periods were 3[733] and 4[734] days.

Table 176 summarizes the data used to calculate the weighted mean and weighted standard deviation for a lognormal distribution,[735] along with the weights (which equal the number of cases).

The bottom three rows come from the 22 cases of aspiration infection reported by Chierakul et al. The values in the table are our interpretation of the information presented. Specifically, the last row has high uncertainty associated with it, as discussed previously. Based on the numbers as shown in Table 176, the weighted mean and standard deviation are 4.8 and 5.8 days, respectively. If the bottom three rows are removed, the result becomes 5.1 and 2.7 days. To better reflect the fact that the incubation period ranges widely, we include all data in Table 176 for the final model: a lognormal distribution with a mean of 4.8 and standard deviation of 5.8 days.

Injury Profile

MABW aptly summarizes difficulty in describing the symptoms of melioidosis:

> Melioidosis, which presents as a febrile illness, has an unusually broad range of clinical presentations that has resulted in various classifications of melioidosis, none of which are considered satisfactory. However, clinical disease with *B. pseudomallei* is generally caused by bacteria spread and seeding to various organs within the host. The diversity of infectious presentations includes acute localized suppurative soft tissue infections, acute pulmonary infections, acute fulminant septicemia, and chronic localized infections.[736]

A summary of the clinical symptoms is as follows:

> The most frequent clinical picture is a septicaemic illness, often associated with bacterial dissemination to distant sites such that concomitant

732 Ko et al., “Melioidosis Outbreak after Typhoon,” 897.

733 Green and Tuffnell, “Laboratory Acquired Melioidosis,” 599.

734 Schlech et al., “Laboratory-Acquired Infection,” 1134.

735 Lognormal distribution is the standard for incubation period when the data do not indicate otherwise. See: Hiroshi Nishiura, “Early Efforts in Modeling the Incubation Period of Infectious Diseases with an Acute Course of Illness,” *Emerging Themes in Epidemiology* 4 (2007): 12 pp.

736 Vietri and Deshazer, “Melioidosis,” 153.

> pneumonia and hepatic and splenic abscesses are common. Bacteraemia and pneumonia occur in 50% of cases, but not necessarily together. Pulmonary involvement may involve the lung parenchyma and/or pleural cavity and may result in abscess formation. Solitary or multiple abscesses may develop in the liver and/or spleen. Hepatosplenic abscess formation is reported to be present in a quarter of melioidosis patients in Thailand, but in only 6% of melioidosis patients in Australia. Multiple abscesses are more common than a solitary abscess in either organ. The finding of a "Swiss cheese" appearance on ultrasonogram or "honeycomb" appearance on computed tomography (CT) scan are said to be highly suggestive of melioidosis. More than half of the patients with hepatosplenic abscess(es) lack abdominal pain or tenderness.[737]

Standard symptoms for melioidosis are thus difficult to define, but *MABW* does state the following, which is consistent with pneumonia:

> Patients with acute pulmonary melioidosis present with cough, fever, sputum production, and respiratory distress, and they can present with or without shock.[738]

The 20-year Darwin Study also provides useful information because the report summarizes clinical findings from 540 patients. It reports that in over 50% of patients, the primary presentation was pneumonia and that another common symptom listed was abscesses, which can be in almost any external area or internal organ, including neurological, splenic, liver, prostatic, parotid, and inter-abdominal. For the 278 patients with pneumonia, those with septic shock had a 49% case fatality rate even with medical treatment, whereas those without septic shock had only a 6% case fatality rate,[739] suggesting that the primary difference between survivors and nonsurvivors is the development of septic shock. The report also notes that "secondary foci of infection are common in melioidosis […], presumably from bacteremic spread and reflecting the high rate of bacteremia overall (55%),"[740] implying that the secondary symptoms related to bacteremia spread were developed later. Taking all the information in this paragraph together, it seems reasonable to split the model into two stages, with the second stage being different for survivors and non-survivors—either they develop septic shock (secondary to bacteremic spread) and die, or they do not and they recover.

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737 Limmathurotsakul and Peacock, "Melioidosis: A Clinical Overview," 129–130.

738 Vietri and Deshazer, "Melioidosis," 153.

739 Currie, Ward, and Cheng, "The Epidemiology and Clinical Spectrum of Melioidosis," 3 (Table 2).

740 Ibid., 9.

A large-scale attack using *B. pseudomallei* would almost certainly come in aerosol form. Although the route of infection is not recorded in the broad-based historical studies cited previously, in the two cases of lab infection (believed to be aerosol) and the six tsunami victims who probably aspirated infected water, all had *pleuritic* pneumonia as the primary presentation. Further, the authors of the 20-year Darwin Report stated that "the association between inhalation as a route of acquisition and increased severity of disease … appears to have been under-appreciated in melioidosis."[741] Both pieces of information just cited suggest that it would be wise to assume that the disease of interest for *AMedP-7.5*—disease caused by inhalation of *B. pseudomallei*—is of higher severity than the disease represented in most clinical case reports.

On that basis, the first stage of disease includes *severe* chest pain and *severe* respiratory distress, in addition to the other signs/symptoms of fever, sputum-producing cough malaise, fatigue, chills, abscesses, and bacteremia. Although we recognize that *many* other symptoms may also be present, these symptoms seem to be the best general representation of acute pulmonary melioidosis. The symptoms just described would seem to fit well with Injury Severity Level 3 (Severe).

The second stage of disease is characterized by either gradual recovery from the Stage 1 symptoms, modeled as Injury Severity Level 2 (Moderate), or the onset of septic shock secondary to bacteremic spread, leading to death (Injury Severity Level 4, Very Severe).

Table 177 summarizes the melioidosis Injury Profile.

Table 177. Melioidosis Injury Profile

	Stage 1	Stage 2 (Survivors)	Stage 2 (Non-Survivors)
Signs and Symptoms (S/S)	Sputum-producing cough, fever, severe (pleuritic) chest pain, severe respiratory distress, malaise, fatigue, chills, abscesses, bacteremia	Gradual recovery from Stage 1 symptoms	Stage 1 symptoms plus septic shock secondary to bacteremic spread
S/S Severity	3 (Severe)	2 (Moderate)	4 (Very Severe)

Duration of Illness

Retrospective studies have not provided good statistical data on the duration of illness, even if the data pool is not narrowed down as specified in Section 0. Most review articles

741 Ibid., 7.

discuss all forms of the disease and the general population, which is not ideal for the present purpose.

The USAMRIID report on RMs and AGMs states that the results are typical for humans after respiratory exposure by aspiration or inhalation and describes fulminant pulmonary infection and sepsis, with many becoming moribund 3 to 5 days after exposure.[742] The report on the marmoset experiment by Porton Down experts similarly states that their result, death within a few days, is consistent with human data.[743] Neither report describes the specific human data to which their results were compared, so the basis for their claims is unclear. We preferred to use the human data, flawed as they are.

Without relaxing the restrictions on the data pool listed in Section 0, no data are available to parameterize the duration of illness submodels. Table 178 summarizes sources that provide data on each stage of illness required for the model, in addition to the data relevance issues for each source. Note that each source has at least one issue and that to develop models for each stage, all three of the data restrictions listed in the table must be relaxed. The restriction on route of exposure is not listed explicitly in Table 178 because its effect on the duration of illness is already included in the requirement for pulmonary symptoms ("presentation").

Relaxing the data restrictions has a complicated effect on the estimate of casualties and the burden on the medical system. Since the disease is generally more severe in patients with risk factors, including these patients likely shortens the overall duration until death in non-survivors but increases duration of recovery in survivors. Including patients who receive medical treatment likely increases the time until death in non-survivors and decreases the recovery time for survivors. Note that the expected effects of including medical treatment are opposite the expected effects of including patients with risk factors. The effect of allowing patients without pulmonary symptoms is unclear because no data are available on the relative courses of illness for patients with and without pulmonary symptoms. Since there may be some cancellation of effects, the net effect of including data from patients with risk factors, patients who received medical treatment, and patients without pulmonary symptoms may not be large. In truth, it is unknown, but allowing these data was necessary to enable the development of a model. Table 179 summarizes the data from the sources identified in Table 178. In addition to the table data, the total duration of hospitalization in the two laboratory-acquired cases was 47 and 32 days.[744]

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742 Yeager et al., "Natural History of Inhalation Melioidosis," 3338.

743 Nelson et al., "Development of an Acute Model," 428.

744 Green and Tuffnell, "Laboratory Acquired Melioidosis"; Schlech et al., "Laboratory-Acquired Infection."

Table 178. Summary of Available Duration of Illness Information and Relevance Issues

Source	Stage 1	Survivor Stage 2	Non-Survivor Stage 2	Data Relevance Issues[a]
Simpson		X	X	Risk factors, presentation, medical treatment
Chetchotisakd		X	X	Risk factors, presentation, medical treatment
Chierakul			X	Medical treatment
Chan	~X[b]	X	X	Risk factors, presentation
Ko	X			Risk factors, medical treatment
Currie, Ward, and Cheng			X	Risk factors, medical treatment

Note: See Appendix B for full reference citations.

[a] Risk factors: either the percentage of patients with risk factors is unknown, or it is greater than 50%. Presentation: either the percentage of patients with primarily pulmonary symptoms is unknown, or it is less than 50%. Medical treatment: either the percentage of patients who received appropriate medical treatment is unknown, or it is greater than 50%.

[b] This source describes time spent in the general ward and time spent in the ICU. It does not specifically address the early stages of illness, but, if no other data were available, the general ward could be used as a surrogate for Stage 1.

Given the format of the available data, the recommended distribution type for each stage of illness is a PERT distribution.[745] A PERT distribution is characterized by a *median* (not *mean*) value, a minimum value, and a maximum value. This distribution type is helpful, given the available data, because there is no clear method by which to calculate a mean and standard deviation that uses all or most of the data.[746] Note that while some of the ranges listed in Table 179 are likely so wide because of a small fraction of outliers, the PERT distribution naturally emphasizes the expected value over the fringes, so the impact of the outliers is not expected to be unduly large. In any case, melioidosis is a notoriously variable disease, so a wide range of times is warranted.

745 One could also choose a triangle distribution, but our preference is PERT. Our choice is arbitrary.

746 The only stage for which mean and standard deviation data are available is Stage 2 for survivors, and that data come from a single report. It is preferable to combine the results from several reports, where possible.

Table 179. Specific Data on the Duration of Individual Stages of Illness

Parameters	Stage 1 Days (# patients)	Stage 2 Survivors Days (# patients)	Stage 2 Non-Survivors Days (# patients)
Mean		18.5 (*n* = 50)[c] 21.2 (*n* = 50)[c]	
Std. Dev.		10.7 (*n* = 50)[c] 1.4 (*n* = 50)[c]	
Median	4 (*n* = 21)[a]	11 (*n* = 14)[a] 16 (*n* = 50)[c] 19 (*n* = 50)[c] 14 (*n* = 70)[d] 15 (*n* = 76)[d]	2 (*n* = 13)[a] 4 (*n* = 14)[e] 3 (*n* = 75)[f]
Range	1–10 (*n* = 21)[a]	1–26 (*n* = 14)[a] 5–43 (*n* = 70)[d] 2–47 (*n* = 76)[d]	0–13 (*n* = 13)[a] 1–16 (*n* = 14)[e] 0–111 (*n* = 75)[f]
Interquartile Range		11–18 (*n* = 70)[d] 10–20 (*n* = 76)[d]	1–7 (*n* = 14)[e]
Other	≤ 1 (*n* = 13/40)[b] ≤ 3 (*n* = 25/40)[b] > 3 (*n* = 15/40)[b]		≤ 2 days (n = 49/103)[d]

[a] From Chan et al., "Clinical Characteristics and Outcome."

[b] From Ko et al., "Melioidosis Outbreak after Typhoon."

[c] From Chetchotisakd et al., "Randomized, Double-Blind, Controlled Study."

[d] From Simpson et al., "Comparison of Imipenem and Ceftazidime."

[e] From Chierakul et al, "Melioidosis in 6 Tsunami Survivors."

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

For Stage 1, there are relatively little data. Chan et al. state that their data are based on the length of stay in the general ward of the hospital for patients who later ended up in the ICU. The stage in the disease that these patients were actually in is uncertain since no other details are reported. The other Stage 1 data, from Ko et al., give a general idea of the range, with 63% of patients reporting prodromes of less than 3 days and about half of those patients reporting within 1 day. However, the full distribution is unknown.

Since the Ko et al. dataset is based on actual prodromes, we considered it more representative of the target model. We had to approximate the numbers to enable use of the data to generate parameters for the PERT distribution. Since the time resolution in *AMedP-7.5* is 1 day, we assumed that the 12 cases of 2- or 3-day duration were split evenly between the two options: six cases at 2 days, and six cases at 3 days. Regardless of the exact values, in the other 28 cases, 13 are lower (≤1 day) and 15 are higher (>3 days), so the median value of the full dataset will always be 3 days. The reported range of 1 to 10 days from Chan et al. seemed reasonable; therefore, since no data are available to support an

alternative range, the PERT distribution parameters for Stage 1 are a median of 3 days and a range of 1 to 10 days.

For the duration of Stage 2 for survivors, we did not directly use the mean and standard deviation data from Chetchotisakd et al. because these data come from a single report. We did use the medians from their report. The weighted arithmetic mean of the five reported medians is 15.5 days. The combined range is 1 to 47 days. Consistent with that range, the mean plus three standard deviations from the Chetchotisakd et al. data is about 51 days. Thus, the PERT distribution parameters for Stage 2 Survivors are a median of 15.5 days and a range of 1 to 47 days. The report by Simpson et al. that the interquartile ranges in their patients were 11–18 and 10–20 days is consistent with the emphasis the PERT distribution places on the median value.

For the duration of Stage 2 for non-survivors, all the data in Table 179 indicate a rather short time, with the exception of the range of 0 to 111 days reported by Currie, Ward, and Cheng. Assuming one or a few patients with abnormally long courses of illness heavily skewed their range, a range of 0 to 16 days seems more reasonable, based on the data from Chan et al. and Chierakul et al. The weighted arithmetic mean of the three medians listed in Table 179 is 3.0 days. Thus, the PERT distribution parameters for Stage 2 non-survivors are a median of 3.0 days and a range of 0 to 16 days. This relatively short duration (compared with survivors) makes sense, given that the difference between the two groups is septic shock. The specific values are also is consistent with the interquartile range of 1 to 7 days reported by Chierakul et al. The result is slightly longer than that in the statement by Simpson et al. that 49 of their 103 patients died within 2 days of admission.

Table 180 summarizes the PERT parameters. The laboratory cases fall on the longer end of the curve for survivors. The distributions also generally represent the Table 179 data well, despite a few discrepancies. However, none of the data used to derive these distributions meet the criteria specified in Section 0. The various data pool restrictions were relaxed to facilitate development of the models, so these models must be considered placeholders until other data become available.

Table 180. PERT Parameters for Melioidosis Duration of Illness Model

	Stage 1 (All)	Stage 2 (Non-Survivors)	Stage 2 (Survivors)
Minimum	1.0	0	1.0
Maximum	10	16	47
Median	3.0	3.0	15.5
PERT mean (μ)[a]	3.8	4.7	18.3

PERT parameter 1 (α)[a]	1.9	1.8	2.3
PERT parameter 2 (β)[a]	4.1	4.3	3.7

[a] Calculated from the minimum, maximum, and median.

Medical Countermeasures and Treatment Model

"There is no licensed vaccine available to prevent human melioidosis and no definitive evidence that infection with *B. pseudomallei* confers immunity."[747] Treatment focuses on antibiotics. Aggressive and appropriate antibiotic therapy must begin immediately upon suspicion of the disease (even before culture confirmation, which takes 2 to 3 days[748]). The treated model incorporates a generic effect of antibiotic treatment, which can significantly reduce the case fatality rate and reduce the duration of illness.[749] There is also evidence that effective intensive care may be equally important in reducing mortality.[750]

The data filters described in Section 0 must also be applied here (with the obvious exception that medical treatment is now relevant). That is, data on the effect of medical treatment must also ideally be limited to people with no risk factors who had pulmonary symptoms. Aside from the changes to the lethality and duration of illness models described in the following subsections, the untreated and treated models are the same.

Lethality

The 20-year report on the Darwin study provides both context and some specific data that are useful as a starting point for estimating a CFR for the treated model. For context, the authors state, "Melioidosis should be seen as an opportunistic infection that is unlikely to kill a healthy person, provided infection is diagnosed early and resources are available to provide appropriate antibiotics and critical care."[751] Table 1 of the report shows that only 2 of the 106 patients who had no known risk factors died (and those 2 were elderly, which is actually a risk factor as defined in Table 3 of the same report). The authors do not provide information on the fraction of the 106 patients who had pulmonary symptoms. They do show that even when patients with risk factors are included, the fatality rate was only 6% for those with pneumonia without septic shock. Since the median soldier has no risk factors and is therefore not expected to have septic shock, the logical assumption is that the case fatality rate for soldiers who receive medical treatment should be less than 6%.

Two reports give lethality data for actual troop populations. The first, summarized in Table 175, shows that U.S. troop populations that received appropriate medical treatment

747 Vietri and Deshazer, "Melioidosis," 158.
748 Inglis, Rolim, and Rodriguez, "Clinical Guideline," 1.
749 Cheng and Currie, "Melioidosis: Epidemiology, Pathophysiology, and Management," 403.
750 Currie, Ward, and Cheng, "The Epidemiology and Clinical Spectrum of Melioidosis," 9.
751 Ibid., 1.

in the late 1960s had a CFR from 2% to 6%.[752] The population in the second report is Singaporean troops who received medical treatment between 1988 and 1994 and had a case fatality rate of 4 out of 23, or 17%.[753] The disparity is unexpected. Because details of the treatment provided are not described in either source, it is possible that differences in treatment are the explanation, although this explanation seems unlikely since the Singaporean data are about 20 years later than the U.S. data. Another possibility is different strains of bacteria, which we do not propose to account for in the models. If the three datasets—Darwin patients with no risk factors (n = 104, 0 deaths), U.S. troops 1967–1970 (n = 195, 6 deaths), and Singaporean troops (n = 23, 4 deaths)—are combined, the overall case fatality rate is about 3%. Thus, the recommended case fatality rate for the treated model is 3%. This value is consistent with the statement by the authors of the 20-year report on the Darwin Study that melioidosis is unlikely to kill a healthy person.

Duration of Illness

For melioidosis, the treatment regimen comprises an initial elimination treatment followed by a maintenance regimen. The typical elimination treatment requires IV delivery of drugs every 6 to 8 hours for 2 weeks.[754] After this treatment ends there is an oral eradication therapy regimen that typically lasts 3 to 6 months,[755] during which time troops would be capable of their duty and would only need to take antibiotic pills as prescribed to complete their recovery. Thus, casualties can RTD 2 weeks after they begin receiving antibiotic treatment.[756] Note that when the casualties RTD, commanders must consider the logistic support they need for the oral eradication therapy when making mission deployment decisions, or the casualties are likely to relapse.[757]

Model Summary

Table 181 and Table 182 summarize the model parameters for melioidosis used in *AMedP-7.5*. While the parameters in these tables represent current best estimates, any new data that become available, particularly for inhalational exposure in humans without risk factors, would improve the model.

752 Neel, *Medical Support*, 44.

753 Lim et al., "Burkholderia pseudomallei Infection in the Singapore Armed Forces," Table 3.

754 Wiersinga, Currie, and Peacock, "Melioidosis," 1041 (Table 1).

755 Ibid., 1041.

756 As stated in Section 0, any potential administrative decision to leave soldiers on the maintenance regimen off duty is not considered here.

757 Simpson et al., "Comparison of Imipenem and Ceftazidime," 386; Limmathurotsakul and Peacock, "Melioidosis: A Clinical Overview," 135–136.

Table 181. Melioidosis Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 15 CFU Probit slope = 3.5 probits/log (dose)
Lethality		
• Untreated	Rate	28%
• Treated	Rate	3%
Incubation period	Lognormal distribution	Mean = 4.8 days Standard deviation = 5.8 days μ = 1.118; σ = 0.949
Duration of illness		
• Stage 1	PERT distribution	Minimum = 1 day Median = 3 days Maximum = 10 days μ = 3.8; α = 1.9; β = 4.1
• Stage 2 (survivors)	PERT distribution	Minimum = 1 day Median = 15.5 days Maximum = 47 days μ = 18.3; α = 2.3; β = 3.7
• Stage 2 (non-survivors)	PERT distribution	Minimum = 0 days Median = 3 days Maximum = 16 days μ = 4.7; α = 1.8; β = 4.3
• Total duration after initiation of antibiotics (treated survivors)	Constant	Two weeks after initiation of medical treatment, whether in Stage 1 or 2.

Table 182. Melioidosis Injury Profile

	Stage 1	Stage 2 (Survivors)	Stage 2 (Non-Survivors)
S/S	Sputum-producing cough, fever, severe (pleuritic) chest pain, severe respiratory distress, malaise, fatigue, chills, abscesses, bacteremia	Gradual recovery from Stage 1 symptoms	Stage 1 symptoms plus septic shock secondary to bacteremic spread
S/S Severity	3 (Severe)	2 (Moderate)	4 (Very Severe)

Cohorts and Special Considerations (*AMedP-7.5 Section 5.2.4.3*)

The definitions of the cohorts are sufficiently explained in *AMedP-7.5*. This section explains the equations used to calculate the cohort populations; for definitions of the variables in the equations, see *AMedP-7.5*.

Equation 5-51:

$$F_U = E \cdot p_{f\text{-}U}(meli) \cdot \sum_{d=1}^{d_{trt\text{-}meli}} PDT_{5\text{-}44}(d)$$

Total who will die; Total # of ill; Fraction already dead

Equation 5-52:

$$S_U = E \cdot \left(1 - p_{f\text{-}U}(meli)\right) \cdot \sum_{} PDT_{5\text{-}45}(d)$$

Total who will not die; Total # of ill; Fraction already RTD

Equation 5-53:

$$F_{T\text{-}WIA} = E \cdot p_{f\text{-}T}(meli) \cdot \left(1 - \sum_{d=1}^{d_{trt\text{-}meli}} PDT_{5\text{-}42}(d)\right)$$

Total who will die; Total # of ill; Fraction not yet ill

Equation 5-54:

$$S_{T\text{-}WIA} = \frac{F_{T\text{-}WIA} \cdot \left(1 - p_{f\text{-}T}(meli)\right)}{p_{f\text{-}T}(meli)}$$

Ratio of (1-CFR) to CFR converts non-survivors to survivors

Equation 5-55:

$$F_{T\text{-}2} = p_{f\text{-}T}(meli) \cdot \left(\left(E \cdot \sum_{} PDT_{5\text{-}43}(d)\right) - (F_U + S_U)\right)$$

CFR; Total who have entered Stg 2; Total who completed Stg 2 before treatment began

Equation 5-56:

$$S_{T\text{-}2} = \frac{F_{T\text{-}2} \cdot \left(1 - p_{f\text{-}T}(meli)\right)}{p_{f\text{-}T}(meli)}$$

Ratio of (1-CFR) to CFR converts non-survivors to survivors

Equation 5-57:

$$F_{T\text{-}1} = \left(E - (F_U + S_U + F_{T\text{-}WIA} + S_{T\text{-}WIA} + F_{T\text{-}2} + S_{T\text{-}2})\right) \cdot p_{f\text{-}T}(meli)$$

Total # of ill; Everyone not treated while in Stage 1…; … who will d

Equation 5-58:

$$S_{T\text{-}1} = \frac{F_{T\text{-}1} \cdot \left(1 - p_{f\text{-}T}(meli)\right)}{p_{f\text{-}T}(meli)}$$

Ratio of (1-CFR) to CFR converts non-survivors to survivors

1.23. Plague Model
(*AMedP-7.5 Sections 5.2.5 and 5.2.6*)

Introduction

Yersinia pestis, the causative agent of plague, is a rod-shaped, non-motile, non-sporulating, gram-negative, bipolar staining, facultative anaerobic bacterium that grows well on commonly used laboratory media. Plague, a zoonotic disease, is transmitted from rodents and has resulted in at least three global pandemics.[758] The bubonic form of the disease is spread to humans by fleas that live on plague-infected rodents. Septicemic plague typically follows from untreated bubonic plague, but may result directly from a flea bite. The pneumonic form of the disease may develop from bubonic plague and would likely be the primary form resulting after purposeful aerosol dissemination of the organisms. Pneumonic plague, the form of the disease modeled in *AMedP-7.5*, is contagious among humans and is the most fatal form.

Assumptions and Limitation (*AMedP-7.5 Sections 5.2.5.2 and 5.2.6.2*)

Assumption: The disease resulting from exposure to *Y. pestis* is pneumonic plague.

This assumption is consistent with the assumption of aerosol dissemination that is one of the core assumptions of *AMedP-7.5*.

Assumption: Untreated pneumonic plague is 100% lethal.

Supporting reasoning is given in Subsection 23.B.2.

Limitation: Although the model requires the user to specify a day on which antibiotic treatment becomes available ($d_{trt\text{-}plag}$), it does *not* apply treatment to every person on that day; only those who have been declared WIA are modeled to begin receiving antibiotics on that day. Those who are declared WIA after $d_{trt\text{-}plag}$ are modeled to begin receiving antibiotics on the day they are declared WIA.

Although this is stated as a limitation, it is actually the most sensible way to apply treatment.

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758 Patricia L. Worsham et al., "Plague," chap. 5 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), 92–93.

Human Response Model (*AMedP-7.5 Tables 5-48 to 5-50, and 5-56 to 5-57*)

Infectivity

Naturally, human data to inform this model are not available. Although there are data on many other animal models, we assume that NHPs are the most suitable model of humans for this aspect of pneumonic plague; this section only discusses the available NHP data.

Because the pneumonic plague is almost uniformly lethal, plague research generally focuses on lethality as opposed to infectivity. However, dose-dependent *lethality* does not make sense for an infectious agent except in the scenario of a 100% CFR—when a source states an LD_{50}, we interpret that to mean that they have assumed or observed a 100% CFR but are actually reporting an ID_{50}. Thus, this section will summarize a number of reported "LD_{50}" values, but will conclude with a selected ID_{50}.

One commonly cited LD_{50} estimate, 2×10^4 cells,[759] is based on inhalation experiments with RMs.[760] However, the estimate appears to be based on experiments with a combination of unvaccinated and vaccinated animals. Although the vaccine did not fully protect the animals, the difference in mortality between unvaccinated and vaccinated RMs indicates some degree of efficacy; the LD_{50} estimate from the paper cannot be used because it is skewed by a medical countermeasure.

AGMs have been found to be so sensitive to *Y. pestis* that even strains used in live vaccines can cause infection; sources such as Welkos et al.[761] are not relevant for the infectivity model. Likewise, RMs have been found to have a pneumonic disease that differs significantly from the disease in humans, so it is not clear that they are a suitable model for infectivity.[762] With the endorsement of participants at a joint Food and Drug Administration and National Institute of Allergy and Infectious Disease symposium, Van Andel et al. conducted a study to determine whether CMs are a suitable model for humans,

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759 Although the authors stated the value in units of "cells," it is also sometimes reported with units of CFU.

760 R. S. Speck and H. Wolochow, "Studies on the Experimental Epidemiology of Respiratory Infections: Experimental Pneumonic Plague in *Macacus rhesus*," *Journal of Infectious Diseases* 100, no. 1 (1957): 59.

761 S. L. Welkos et al., "Studies on the Contribution of the F1 Capsule-Associated Plasmid pFra to the Virulence of *Yersinia pestis*," *Contributions to Microbiology and Immunology* 13 (1995): 299–305.

762 Roger Van Andel et al., "Clinical and Pathologic Features of Cynomolgus Macaques (*Macaca fascicularis*) Infected with Aerosolized *Yersinia pestis*," *Comparative Medicine* 58, no. 1 (2008): 68.

concluding, "Indonesian cynomolgus macaques appear to offer an excellent model for studying human pneumonic plague."[763]

Van Andel et al. exposed 22 Indonesian-origin cynomolgus macaques to doses ranging from 12 to 42,700 CFU of *Y. pestis*. Seventeen developed plague,[764] two of which with no premonitory signs or symptoms, and the remaining five remained plague-free—with no bacteriologic, gross, or histologic evidence of plague infection—at doses less than 250 CFU. One of the plague-free CMs was euthanized on the basis of symptoms, but was confirmed to not have plague by bacteriologic, gross, and histologic investigation. Using a logistic regression, Van Andel et al. calculated an ID_{50} of 66 CFU.[765]

Because Van Andel et al. did not report a probit slope, we conducted our own probit analysis. Table 183 summarizes the infectivity data extracted from Van Andel et al. Our probit analysis yields the following results: ID_{50} of 67 CFU (95% CI 0–172) and PS of 1.8 probits/log (dose) (95% CI 0.2–3.4). Thus, *AMedP-7.5* uses the ID_{50} reported by Van Andel et al., 66 CFU, and the probit slope we calculated, 1.8 probits/log (dose).

Table 183. *Y. Pestis* CM Inhalation Infectivity Data from Van Andel et al.

Dose (CFU)	CM Infected?	Dose (CFU)	CM Infected?	Dose (CFU)	CM Infected?
12	No	208	Yes	759	Yes
16	No	227	No	3,050	Yes
35	Yes	262	Yes	4,410	Yes
58	No	264	Yes	4,850	Yes
122	Yes	295	Yes	12,400	Yes
169	Yes	353	Yes	42,700	Yes
174	Yes	374	Yes		
198	No	479	Yes		

Source: Van Andel et al., "Clinical and Pathologic Features," Tables 2, 70. Note that the first paragraph under "Results" provides necessary context and explanation of what is presented in Table 2.

Lethality

Evidence indicates that once infected, individuals who remain untreated will likely die. "The reported case fatality rate is close to 100%."[766] Additional studies have shown

763 Ibid., 74.

764 Of these, 2 died "naturally" and the other 14 were euthanized after developing a fever of at least 39.7°C, which has been found to be a strong indicator that the animals will die within 48 hours. See Van Andel et al., "Clinical and Pathologic Features," 69.

765 Van Andel et al., "Clinical and Pathologic Features," Tables 2 and 5.

766 Raymond Gani and Steve Leach, "Epidemiological Determinants for Modeling Pneumonic Plague Outbreaks," *Emerging Infectious Diseases* 10, no. 4 (April 2004): 609.

similar results—all animals, either monkey or murine, showing symptoms of infection eventually die as a result of the infection if untreated.[767] Thus, *AMedP-7.5* models a 100% CFR for pneumonic plague.

Incubation Period

This model is borrowed from work done by Gani and Leach, who noted that the available data on human cases of primary pneumonic plague are quite limited due the nature of outbreaks.[768] However, they found six sources that provided some information and performed a meta-analysis. Since we were unable to acquire some of the sources to perform our own analysis, we rely on the Gani and Leach model. Gani and Leach do not state the exact number of data points on which the model is based, but based on their Figure 1 (a frequency plot), it appears to be approximately 40 to 50. Upon fitting a lognormal distribution to the data, they found the mean and standard deviation to be 4.3 days and 1.8 days, respectively, which correspond to $\mu = 1.378$ and $\sigma = 0.402$.

When applied to the SEIPR model, only the mean value of 4.3 days is used. The SEIRP model has two parameters for modeling the incubation period, one of which represents the minimum incubation time. The minimum incubation time included in the data underlying the Gani and Leach model was 1 day (no indication of any cases of *less* than 1 day), so the plague incubation period SEIRP model includes a 1-day minimum with a 3.3-day mean for the second "stage" of incubation implemented using an exponential distribution because of the formulation of the SEIRP model.

Injury Profile

Plague is a biphasic disease, with the end of the prodromal period (modeled as Stage 1) marked by the onset of coughing[769] and the fulminant phase (modeled as Stage 2) ending in death for untreated cases. The following quotations, taken from three different sources, are helpful descriptions of the course of illness:

> [It] progresses rapidly from a febrile flu-like illness to an overwhelming pneumonia with coughing and the production of bloody sputum.[770]
>
> [The prodromal period is] characterized by the sudden onset of severe headaches, chills, malaise, and increased respiratory and heart rates. Body

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767 Wyndham W. Lathem et al., "Progression of Primary Pneumonic Plague: A Mouse Model of Infection, Pathology, and Bacterial Transcriptional Activity," *Proceedings of the National Academies of Science* 102, no. 49 (December 2005): 17786–17791; Jacob L. Kool, "Risk of Person-to-Person Transmission of Pneumonic Plague," *Clinical Infectious Diseases* 40, no. 8 (April 2005): 1166–1172.

768 Gani and Leach, "Modeling Pneumonic Plague Outbreaks," 609.

769 Gani and Leach, "Modeling Pneumonic Plague Outbreaks," 608–609.

770 Robert D. Perry and Jacqueline D. Fetherston, "Yersinia pestis—Etiologic Agent of Plague," *Clinical Microbiology Reviews* 10, no. 1 (January 1997): 58.

> temperature rises steadily during this initial stage…Generally cough [marking the onset of the second stage] develops after 20–24 h, and it is dry at first but becomes progressively productive…over time it becomes increasingly blood-stained and/or purulent. In the final stage (one to several hours before death), the patient produces copious amounts of bright red sputum…[771]

> The onset of the disease is sudden and often marked by rigor. The first stage is characterized by the presence of general signs only; cough is most often still absent; when present, it is usually dry. The prominent symptoms during this period are severe headache, some nausea and vomiting, vertigo and general malaise. Both respiration and pulse show an increased rate; the pulse is early impaired in quality. The temperature, which is but slightly raised at the beginning of the illness, rises steadily during the first stage… The beginning of the second stage is manifested by the appearance of cough or—if this is already present—by that of expectoration. The cough is dry and seldom troublesome at first, but when continuous may exhaust the patient. The sputum shows at first no characteristic appearance, being mainly frothy. Soon, however, there is an admixture with blood, leading to a uniform bright pink or red hue. Now the sputum may be either thin, sometimes frothy or of more syrup-like consistency; but the degree of viscosity typical for croupous pneumonia is not reached. The quantity of bloody sputum varies greatly from mere streaks of red to ounces of deep red blood comparable to that seen in hemorrhage in phthisis (tuberculosis). During the first stage, few if any signs may be detected over the lungs; now symptoms of pneumonia become evident…Death occurs from heart failure. Sometimes there is a marked stage of agony characterized either by more or less protracted coma and symptoms of lung edema or by restlessness and active delirium.[772]

The first stage of illness may include several symptoms, such as fever with cough and dyspnea, including bloody, watery, or purulent sputum, as well as nausea, vomiting, and other gastrointestinal symptoms. The second stage closely resembles other late stage pneumonias.[773]

Based on the above and consistent with Table 2, we assigned Injury Severity Level 2 to the first stage of illness, and an Injury Severity Level of 4 to the second stage of illness. Likewise, we produced the Injury Profile summarized in Table 184. Note that an Injury

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771 Kool, "Risk of Person-to-Person Transmission," 1167.

772 Lien-Teh Wu, *A Treatise on Pneumonic Plague*, C.H.474 (Geneva: League of Nations Health Organization, May 1926).

773 Thomas V. Inglesby et al., "Plague as a Biological Weapon: Medical and Public Health Management," *Journal of the American Medical Association* 283, no. 17 (May 2000): 2283–2285.

Profile for survivors does not exist for pneumonic plague since the model includes a 100% CFR.

Table 184. Untreated Plague Injury Profile

	Stage 1	Stage 2
Signs and Symptoms (S/S)	Severe headache, chills, nausea and vomiting, vertigo and general malaise; increased respiration and heart rates; temperature steadily rises; dry cough begins at the end	Cough becomes progressively more productive, initially with no blood but eventually producing copious amounts of bloody sputum; increased respiratory rate; dyspnea; high temperature; weakness and exhaustion; weak pulse; cyanosis; frequent ataxia; confusion; disorientation; restlessness and active delirium; possibly comatose; eventual circulatory collapse or respiratory failure.
S/S Severity	2 (Moderate)	4 (Very Severe)

Duration of Illness

Analyses of epidemiological data give similar estimates of duration of illness for pneumonic plague. Gani and Leach derived a lognormal distribution with a mean of 2.5 days (standard deviation 1.5 days) from eight outbreaks;[774] Nishiura found a mean of 2.3 days (standard deviation. 1.7 days) using data from the Manchuria outbreak;[775] and Bombardt derived a lognormal distribution with mean of 2.34 days (standard deviation 1.07 days) from the Manchuria outbreak.[776]

Bombardt pointed out that in the cases of the 1965 Vietnam and 1997 Madagascar outbreaks, antibiotic treatments were employed, and he speculated that the range in means and standard deviations may be due in part to differences in sample size and *Y. pestis* strain. These differences could perhaps explain the difference in means between the estimates of Bombardt and Gani and Leach for overlapping data.

Based loosely on the distributions mentioned above, *AMedP-7.5* models the total duration of illness with a lognormal distribution with a mean of 2.5 days and a standard deviation of 1.2 days. As for when the transition from Stage 1 to Stage 2 occurs, the quotations in the Injury Profile Subsection (0) all acknowledge that the disease progresses rapidly, with the onset of a dry cough and shortly thereafter the change to a wet cough marking the beginning of Stage 2 (according to the Injury Profile) occurring around 20 to

774 Gani and Leach, "Modeling Pneumonic Plague Outbreaks," 609.

775 Hiroshi Nishiura et al., "Transmission Potential of Primary Pneumonic Plague: Time Inhomogeneous Evaluation Based on Historical Documents of the Transmission Network," *Journal of Epidemiology Community Health* 60 (2006): 643.

776 Bombardt, *Primary Pneumonic Plague Transmission*.

24 hours post-onset.[777] This is also consistent with the *JAMA Consensus Statement on Plague* statement that "the fatality rate of patients with pneumonic plague when treatment is delayed more than 24 hours after symptom onset is extremely high,"[778] indicating significant progression of the disease that cannot be stopped by antibiotics.

Thus, for both the isolation/quarantine model and the SEIRP model, the first stage is modeled with a constant length of 1 day. The isolation/quarantine Stage 2 duration of illness model is therefore a lognormal distribution with mean 1.5 days and standard deviation 1.2 days, corresponding to $\mu = 0.158$ and $\sigma = 0.703$. The SEIRP model only incorporates the mean time of 1.5 days for Stage 2, and because of the formulation of the SEIRP model the mean is implemented using an exponential distribution.

Contagious Spread Parameters for the SEIRP Model

The two parameters for which values must be derived are α (single value) and β (function of time post-incident).

The Relative Infectiousness (α)

In reviewing the Manchurian epidemic cases, Kool found that there is an early period of disease during which patients were noncontagious or "non-infective," and that only after the late stage of the disease onset, did individuals become infectious.[779] A source cited by Kool states that "owing to the absence of cough and expectoration during the first stage of the disease, patients are practically non-infective."[780]

Summarizing prior research, Kool indicates that coughing appears to be the primary method by which aerosolized plague is spread; only a very limited fraction (1 of 39) of the sampled non-coughing patients respired plague bacteria that could be captured and grown on a culture plate.[781]

Based on the above findings, we set α equal to zero for plague. In the model, this prevents any person in Stage 1 of disease (I_1 cohort) from spreading disease to the S cohort. All contagious spread in the model will occur as a result of the I_2 cohort.

The Time-Varying Rate of Disease Transmission (β)

The SEIRP model presumes that a time-varying disease transmission rate β is at the disposal of the modeler. The rate of disease transmission is essentially the product of (1) the conditional probability of infection (given an "adequate" contact) and (2) the number

777 Kool, "Risk of Person-to-Person Transmission," 1167.

778 Inglesby et al., "Plague as a Biological Weapon," 2286.

779 Kool, "Risk of Person-to-Person Transmission," 1167–1168, citing Wu, *A Treatise on Pneumonic Plague*.

780 Wu, *A Treatise on Pneumonic Plague*.

781 Kool, "Risk of Person-to-Person Transmission," 1170.

of adequate contacts per unit time. Both the conditional probability of infection and the rate of adequate contacts can change as an epidemic unfolds. For example, the conditional probability of infection can vary during an epidemic if the disease-causing microorganism mutates and becomes more or less able to overcome the host's defensive mechanisms. Perhaps more important, the contact rate tends to fluctuate with day-to-day human activities, a growing public awareness of an ongoing outbreak, behavioral modifications due to this awareness, etc.

The time dependence of disease transmission is unknown a priori. But the epidemic curve (number of new cases per unit time) and other epidemiological information from a pertinent historical outbreak can be used in conjunction with an appropriate epidemic model to quantify the causative time-varying transmission rate. By assumption, such a derived historical transmission rate is representative of what could happen in a military population.

The 1946 outbreak of primary pneumonic plague in Mukden (now called Shenyang), China, began when a man from another Russian-occupied district arrived in Mukden by train and began his stay with relatives on the 25th of February. He became ill on the 26th and died on the 27th of February. This fatal index case of primary pneumonic plague led to 35 other fatal cases and three nonfatal cases. Because this outbreak did not begin with a precursory case of bubonic plague and a secondary plague pneumonia, and because Mukden was free of plague for the previous 25 years, local medical practitioners did not recognize primary pneumonic plague and they attributed eight deaths (over 10 days) to pneumonia. Even so, under difficult wartime conditions, a thorough (albeit delayed) program of traditional outbreak controls prevented the spread of disease beyond Mukden. In passing, note that a limited quantity of sulfadiazine became available to Mukden physicians 12 days before the outbreak's conclusion (on the 30th of March); all three survivors of primary pneumonic plague were recipients of that drug.[782]

The epidemic curve for the 1946 primary pneumonic plague outbreak in Mukden and data describing the incubation period distribution are sufficient to directly quantify the number of new transmission-caused infections over time. A straightforward back-projection technique[783] and a Monte Carlo algorithm enable this direct quantification. Three basic steps characterize each Monte Carlo trial. First, obtain a random incubation or latent period for every onset of illness (i.e., every new case) that occurs on a given day of the historical outbreak (excluding the index case). Second, backtrack in time to identify when all infections began. And third, compile the total score for each time step. Averaging

782 Bombardt, *Primary Pneumonic Plague Transmission*.

783 Niels G. Becker and Xu Chao, "Dependent HIV Incidences in Back-Projection of AIDS Incidence Data," Statistics in Medicine 13 (1994): 1945–1958.

scores per day for a large number of Monte Carlo trials then yields a mean time-dependent number of new infections that is suitable for use in a deterministic or mean-field derivation of β (this deterministic value is the one used in *AMedP-7.5*).

In deriving β for the historical outbreak of interest, the averaged Monte Carlo results for the number of new transmission-caused infections over time were first inserted into the SEIRP model (in the absence of any medical intervention) and then calculated to obtain the outbreak's S, E, I and R cohorts over time. Quantified S, I_1, and I_2 cohorts, along with averaged Monte Carlo results for the number of new transmission-caused infections over time, were used to calculate the time-varying β. *AMedP-7.5* Table 5-57 shows the derived time dependence of β for the Mukden, China, outbreak.

Medical Countermeasures and Treatment Model

Medical management of pneumonic plague has two main objectives: avoiding mortality via early antibiotic intervention—before symptom onset if possible or as soon as possible thereafter if not—and controlling the risk of contagion. Any patients who survive will likely need extensive supportive care, including respiratory assistance.

Pre-Exposure and Post-Exposure Prophylaxis

Although research in pursuit of a vaccine effective against pneumonic plague in both the United States and the United Kingdom continues, at present, none is available.[784] "The previously available licensed, killed vaccine (manufactured by Greer) was effective against natural bubonic plague, but not against aerosol exposure."[785] Therefore, *AMedP-7.5* does not include vaccination for plague.

Multiple mouse studies have shown ciprofloxacin to be 100% effective in preventing death from pneumonic plague, with other antibiotics having similar or slightly reduced efficacy.[786] Additional independent analysis of the Russel et al. and Byrne mouse data for ciprofloxacin, conducted by Bombardt,[787] and our desire to account for the potential inclusion of other antibiotics that are slightly less effective than ciprofloxacin (in anticipation of logistics shortages in a mass-casualty event) led to the choice of 95% efficacy for the *AMedP-7.5* model. Although the data cited are for pre-exposure

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784 Worsham et al., "Plague," 113.

785 USAMRIID, *Medical Management of Biological Casualties Handbook*, 55.

786 P. Russell et al., "Doxycycline or Ciprofloxacin Prophylaxis and Therapy against Experimental Yersinia pestis Infection in Mice," Journal of Antimicrobial Chemotherapy 37 (1996): 769–774; P. Russell et al., "Efficacy of Doxycycline and Ciprofloxacin against Experimental Yersinia pestis Infection," Journal of Antimicrobial Chemotherapy 41 (1998): 301–305; and William R. Byrne et al., "Antibiotic Treatment of Experimental Pneumonic Plague in Mice," Antimicrobial Agents and Chemotherapy 42, no. 3 (March 1998): 675–681.

787 Bombardt, *Primary Pneumonic Plague Transmission*.

prophylaxis, we assumed the same efficacy would be observed for post-exposure prophylaxis.

Lethality

The *JAMA Consensus Statement on Plague*[788] and *MMBC*[789] both indicate that 24-hours post-onset is a threshold of sorts in terms of the ability of antibiotic treatment to save the life of a pneumonic plague patient. This timing corresponds with Stage 1 of illness in the *AMedP-7.5* model. In *AMedP-7.5*, patients who begin receiving antibiotics while in Stage 1 (or while incubating) have a 0% CFR (and follow a different Injury Profile and duration of illness, as discussed in the following two Subsections), and patients who begin receiving antibiotics while in Stage 2 follow the untreated non-survivor course with a 100% CFR.

Injury Profile

Non-survivors who begin receiving antibiotics in Stage 2 follow the entire Injury Profile in Table 184—the antibiotics are modeled to be completely ineffective. Survivors, whether they began receiving antibiotics during incubation or during Stage 1, follow the Stage 1 Injury Profile described in Table 184. Survivor Stage 2 incorporates the effectiveness of antibiotics, and therefore simply reflects recovery, as indicated in Table 186 (under Subsection 0).

Duration of Illness

For non-survivors, treatment is ineffective and does not alter the duration of illness. *MMBC* indicates that the duration of antibiotic therapy would be "at least 10–14 days."[790] Although antibiotic therapy would initially be administered IM or IV, *MMBC* also indicates that as symptoms improve a patient can be switched to oral antibiotics,[791] at which point a casualty could RTD if needed, so long as the commander remains aware of the individual's need to continue his or her course of treatment. Thus, those who begin receiving antibiotic treatment while in Stage 1 spend 1 day in Stage 1 (same as in the untreated model) and 10 days in Stage 2. During Stage 2, although the overall severity of illness would be consistent with at home care, these patients are assumed to require routine hospitalization to support parenteral administration of antibiotics. Those who begin receiving antibiotics as post-exposure prophylaxis are also assumed to require routine hospitalization for 10 days for the administration of antibiotics, after which they can RTD.

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788 Inglesby et al., "Plague as a Biological Weapon," 2286.

789 USAMRIID, *Medical Management of Biological Casualties*, 55.

790 Ibid., 55.

791 Ibid., 61.

Parameters for the SEIRP Model

Several SEIRP model parameters relate to the medical treatment model. First, parameter μ_{RS}, which is the fixed time individuals spend in the removed survivor, no longer contagious cohort ($R_S(d)$), is 10 days, consistent with the treated duration of illness model. Second, the parameter MT_{I1}, which indicates whether medical treatment causes ill personnel in Stage 1 to no longer transmit disease despite remaining symptomatic (and therefore move into $R_S(d)$), is 1, because antibiotic treatment does have these effects for an individual in Stage 1 of plague.

Model Summary

Table 185 and Table 186 summarize the model parameters for modeling plague with effective isolation/quarantine in *AMedP-7.5*, and Table 187 summarizes the model parameters for modeling plague using the SEIRP model in *AMedP-7.5*. While the parameters in these tables represent current best estimates, any new data that become available, particularly for inhalational exposure in humans (or NHPs, for the infectivity model), may improve the model. Also, a contagious disease model that does not rely on historical outbreaks for modeling the rate of disease spread would be an improvement over the current SEIRP model.

Table 185. Plague Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 66 CFU Probit slope = 1.8 probits/log (dose)
• Pre- or post-exposure antibiotics	Rate (efficacy)	95%
Lethality		
• Untreated or Treatment initiated in Stage 2	Rate	100%
• Treatment initiated in Stage 1	Rate	0%
Incubation period	Lognormal distribution	Mean = 4.3 days Standard deviation = 1.8 days μ = 1.378; σ = 0.402
Duration of illness		
• Stage 1	Constant	1 day
• Stage 2 (non-survivors)	Lognormal distribution	Mean = 1.5 days Standard deviation = 1.2 days μ = 0.158; σ = 0.703
• Stage 2 (treatment initiated in Stage 1)	Constant	10 days
• Total duration (post-exposure prophylaxis)	Constant	10 days

Table 186. Plague Injury Profile

	Stage 1	Stage 2 (non-survivors)	Stage 2 (survivors)
Signs and Symptoms (S/S)	Severe headache, chills, nausea and vomiting, vertigo and general malaise; increased respiration and heart rates; temperature steadily rises; dry cough begins at the end	Cough becomes progressively more productive, initially w/ no blood but eventually producing copious amounts of bloody sputum; increased respiratory rate; dyspnea; high temperature; weakness and exhaustion; weak pulse; cyanosis; frequent ataxia; confusion; disorientation; restlessness and active delirium; possibly comatose; eventual circulatory collapse or respiratory failure.	Cessation of symptoms and return to normal body temperature
S/S Severity	2 (Moderate)	4 (Very Severe)	2 (Moderate)

Table 187. SEIRP Model Parameter Values for Plague

Parameter	Value
$p_E(X_{Q,n}^{eff})$ – Infectivity	See Table 185
ρ_S – efficacy of pre-exposure antibiotics	0.95
ρ_E – efficacy of post-exposure antibiotics	0.95
μ_{E1} – minimum duration of incubation period	1 day
μ_{E2} – mean duration of remainder of incubation period	3.3 days
μ_1 – duration of Stage 1	1 day
μ_2 – mean duration of Stage 2	1.5 days
μ_{RS} – duration of recovery after beginning antibiotics	10 days
α – relative infectiousness	0
$\beta(d)$ – time-varying rate of disease transmission	See *AMedP-7.5* Table 5-57
MT_{I1} – efficacy of medical treatment in Stage 1 of illness	1
$p_f(d)$ – case fatality rate	See Table 185

Isolation/Quarantine Model Cohorts (*AMedP-7.5 Section 5.2.5.3*)

The definitions of the cohorts are sufficiently explained in *AMedP-7.5*. This section explains the equations used to calculate the cohort populations; for definitions of the variables in the equations, see *AMedP-7.5*.

Equation 5-59:	The number of people already dead on $d_{trt\text{-}plag}$
Equation 5-60:	The number of people who have not yet finished incubating
Equation 5-61:	Anyone who finished incubating on the previous day is by definition in Stage 1; whereas anyone who finished incubating any earlier is by definition beyond Stage 1 (either already dead or in Stage 2)
Equation 5-62:	The cohort populations must sum to the total number of ill individuals

1.24. Q Fever Model (*AMedP-7.5 Section 5.2.7*)

Introduction

Q fever is caused by the Gram-negative bacterium *Coxiella burnetii* in the tribe *Rickettsiae*.[792] Q fever is a zoonotic disease, and person-to-person transmission is very rare.[793] The primary animal reservoirs for Q fever are cattle, sheep, and goats. Ticks can also carry the disease, although they are more able to infect animals than humans.[794] Animals, however, do not often show symptoms from the infection, except for an occasional increase in spontaneous abortions.[795] Humans are generally infected by inhaling the organisms let into the air from handling infected animals or their byproducts. *C. burnetii* can survive for several weeks in areas where animals used to be located and can also travel long distances through the air.[796] Therefore, some people can become infected in a city where they do not interact with animals just because of the infectivity and wide dispersal range of the organism.[797] Because it is so hardy when aerosolized, it has been listed as a potential bioweapon.

Assumption and Limitation (*AMedP-7.5 Section 5.2.7.2*)

Assumption: Q fever does not cause any fatalities.

See Subsection 0.

Limitation: Although the model requires the user to specify a day on which antibiotic treatment becomes available ($d_{trt\text{-}Qfvr}$), it does *not* apply treatment to every person on that day; only those who have been declared WIA are modeled to begin receiving antibiotics on that day. Those who are declared WIA after $d_{trt\text{-}Qfvr}$ are modeled to begin receiving antibiotics on the day they are declared WIA.

Although this is stated as a limitation, it is actually the most sensible way to apply treatment.

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792 Leigh A. Sawyer, Daniel B. Fishbein, and Joseph E. McDade, "Q fever: Current Concepts," *Reviews of Infectious Diseases* 9, no. 5 (September–October 1987): 935–946.

793 W. D. Tigertt, A.S. Benenson, and W.S. Gochenour, "Airborne Q Fever," *Microbiology and Molecular Biology Reviews* 25 (September 1961): 285–293.

794 Sawyer, Fishbein, and McDade, "Q Fever: Current Concepts," 935.

795 P. A. Bossi et al., "Bichat Guidelines for the Clinical Management of Q Fever and Bioterrorism-Related Q Fever," *Eurosurveillance* 9, no. 12 (2004): 1–5.

796 M. Maurin and D. Raoult, "Q Fever," *Clinical Microbiology Reviews* 12, no. 4 (October 1999): 518–533.

797 U. Terheggen and P.A. Leggat. "Clinical Manifestations of Q Fever in Adults and Children," *Travel Medicine and Infectious Disease* 5 (2007): 159–164.

Human Response Model (*AMedP-7.5 Tables 5-59 to 5-61*)

Key Literature Summary

While developing the Q fever model, in addition to relying on the relevant *MABW* chapter,[798] we relied heavily on documentation and reports based on experimental data recorded during a series of human and animal tests conducted by William D. Tigertt and colleagues. Much of this information was used in the development of earlier versions of the NATO CBRN casualty estimation methodology (*AMedP-8*). These important source documents are the following:

- Tigertt, William D., "Studies on Q Fever in Man." In J. E. Smadel (ed.), *Symposium on Q Fever* (Washington, DC: Army Medical Service Graduate School, Walter Reed Army Medical Center, Government Printing Office, 1959).
  - Hereafter referred to as Tigertt, "Studies on Q Fever in Man."
- Tigertt, William D. and A. S. Benenson, "Studies on Q Fever in Man." *Transactions of the Association of American Physicians* 69 (1956): 98–104.
  - Hereafter referred to as Tigertt and Benenson, "Studies on Q Fever in Man."
- Tigertt, William D., A. S. Benenson, and W. S. Gochenour. "Airborne Q Fever." *Microbiology and Molecular Biology Reviews* 25 (September 1961): 285–93.
  - Hereafter referred to as Tigertt, Benenson, Gochenour, "Airborne Q Fever."
- George H. Anno et al., *Consequence Analytic Tools for NBC Operations Volume 1: Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B* (*SEB*) *and Q Fever*, DSWA-TR-97-61-V1 (Washington, DC: Defense Special Weapons Agency, October 1998).
  - Hereafter referred to as Anno et al., *Consequence Analytic Tools for NBC Operations*.

Infectivity

Q fever is highly infectious, and even a single organism may be sufficient to cause an infection.[799] Most reports in the literature give infective doses of between 1 and 10

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798 David M. Waag, "Q Fever," chap. 10 in *Medical Aspects of Biological Warfare*, ed. Zygmunt F. Dembek, Textbook of Military Medicine (Washington, DC: Department of Defense, Office of the Surgeon General, U.S. Army, Borden Institute, 2007), 199–213.

799 Sawyer, Fishbein, and McDade, "Q Fever: Current Concepts," 935.

organisms.[800] *MABW* states that a single microorganism can cause an infection, although it does not give specific infective dose values.[801]

In a study designed to establish the infectivity of Q fever in humans, Tigertt, Benenson, and Gochenour[802] exposed guinea pig and human subjects (military research volunteers, or MRVs) to aerosols of *C. burnetii*. The subjects were exposed for 1 minute to aerosol clouds created from various dilutions of a slurry containing approximately 20 billion infectious particles per milliliter. Infection in guinea pigs was diagnosed through serologic studies; infection in humans was diagnosed through serological studies and an onset of clinical symptoms consistent with Q fever, specifically a sustained fever in excess of 100 ºF.

The three Tigertt sources listed under Subsection 0 published data for 29 cases. The *P-8 BMR* also used data on an additional 13 unpublished cases.[803] The three Tigertt sources and the *P-8 BMR* list dose in units of guinea pig intraperitoneal ID_{50}s, or $GPIPID_{50}$, and do not describe how that unit relates to number of *C. burnetii* organisms. However, Ormsbee et al.[804] examined the median infective doses of a variety of rickettsial diseases, and found it to be two organisms for guinea pigs given Q fever via injection. Using this conversion factor and the combined set of 42 data points from the Tigertt articles and the *P-8 BMR*, we generated Table 188.

800 See, for example, Bossi et al., "Bichat Guidelines for the Clinical Management of Q Fever and Bioterrorism-Related Q Fever," and J. D. Hartzell et al., "Q Fever: Epidemiology, Diagnosis, and Treatment." *Mayo Clinic Proceedings* 83, no. 5 (May 2008): 574–579, both of which state that infection can be caused by 1 to 5 organisms; similarly, in K. E. Russell-Lodrigue et al., "*Coxiella burnetii* Isolates Cause Genogroup-Specific Virulence in Mouse and Guinea Pig Models of Acute Q Fever," *Infection and Immunity* 77, no. 12 (December 2009): 5640–5650, the authors note that infection can be caused by as few as 10 organisms.

801 Waag, "Q Fever," 200.

802 Tigertt, Benenson, Gochenour, "Airborne Q Fever."

803 Anno et al., *AMedP-8* (*Biological*) *Methods Report*, 125.

804 R. M. Ormsbee et al., "Limits of Rickettsial Infectivity," *Infection and Immunity* 19, no. 1 (January 1978): 239–245.

Table 188. Human Inhalation Q Fever Infectivity Data as Reported by the *P-8 BMR*

Equivalent $GPIPID_{50}$s	IDA Calculated # Organisms	Humans Exposed	Humans Infected	% Infected
1	2	2	0	0%
10	20	5	2	40%
47[a]	94	4	3	75%
150	300	8	7	87.5%
1,500	3,000	5	5	100%
3,637–3,880	7,274–7,760[b]	8	7	87.5%
15,000	30,000	4	4	100%
23,700–25,529	47,400–51,058[b]	4	4	100%
150,000	300,000	2	2	100%

[a] The Tigertt articles report 3 cases exposed to 50 $GPIPID_{50}$s, whereas the *P-8 BMR* reports 4 cases exposed to 47 $GPIPID_{50}$s. We assume that the Tigertt cases are a subset of the *P-8 BMR* cases and that the *P-8 BMR* value was revised from 50 $GPIPID_{50}$s based on review of the MRV clinical records.

[b] The average of these two values was used for probit analysis

Using probit analysis on the data in Table 188, we derived an ID_{50} of 30 organisms and a probit slope of 0.782 probits/log (dose). This ID_{50} is the same as that reported in the *P-8 BMR*, and the probit slope is nearly identical (and within uncertainty of the estimate). The IDA-derived model is used in *AMedP-7.5*.

Lethality

Death from acute Q fever are rare. *MABW* states that less than 1% of patients will die from the disease,[805] while the *P-8 BMR* did not give information about lethality and assumed that all Q fever patients would recover, even in the absence of treatment.

In their 1999 review of "recently reported epidemiological situations"—outbreaks of Q fever involving several hundred patients throughout the world—Maurin and Raoult found that 1% to 2% of patients died.[806] The percentage of these cases that were treated with antibiotics is unknown. Since Q fever was initially described around the start of the antibiotic era, there are few clinical studies of acute Q fever that did not consider the effects of treatment. In Hornibrook's 1940 study,[807] involving a small number of cases, 1 out of 15 patients died (6.7%). In Derrick's original 1944 study, 3 of 176 untreated cases died

805 Waag, "Q Fever," 202.

806 Maurin and Raoult, "Q Fever," 533.

807 J. W. Hornibrook and K.R. Nelson, "An Institutional Outbreak of Pneumonitis I. Epidemiological and Clinical Studies," *Public Health Reports* 55, no. 43 (October 25, 1940): 1936–1944.

(1.7%),[808] and in a later study that considered much of the same data, 4 of 273 untreated cases died (1.5%).[809]

In cases of chronic Q fever—about 2% of the total reported Q fever infections— death is much more common.[810] In particular, endocarditis is very common in such cases, occurring 60% to 70% of the time, and left untreated has a lethality rate estimated to be as high as 60%.[811]

Even considering chronic cases, the overall lethality rate for diagnosed cases of untreated Q fever is somewhere between 1% and 2%. Because Q fever is assumed to be widely underreported, the true lethality rate is likely even lower. Maurin and Raoult, for example, noted that in many nations Q fever is not a reportable disease, and in many others it is often unreported because the required diagnostic tests are not readily available and confirmatory diagnoses cannot be made.[812] Consequently, *AMedP-7.5* models Q fever as nonlethal.

Incubation Period

The incubation period for Q fever generally lasts a few weeks, although this can depend upon the dose. *MABW* lists an incubation period of between a few days and several weeks.[813] Various clinical case studies of naturally occurring outbreaks provide incubation periods ranging from a few days to a few weeks. For example, in Huebner's study of an outbreak at the National Institutes of Health, the incubation period ranged from 13 to 18 days.[814] In Spelman's study of serological cases from a hospital, four had identified incubation periods of 21, 28, 35, and 39 days.[815] Marrie's study gave different incubation periods for 13 outbreaks, constituting 51 total cases, all due to parturient cats.[816] These incubation periods ranged from 4 to 30 days, with most cases occurring about 14 days after exposure.

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808 E. H. Derrick, "The Epidemiology of Q Fever," *The Journal of Hygiene* 43, no. 5 (April 1944): 357–361.

809 E. H. Derrick, "The Course of Infection with *Coxiella burneti*," *The Medical Journal of Australia* 1, no. 21 (May 26, 1973): 1051–1057.

810 Sawyer, Fishbein, and McDade, "Q Fever: Current Concepts," 936.

811 D. Raoult et al., "Treatment of Q Fever Endocarditis," *Archives of Internal Medicine* 159 (January 25, 1999): 167.

812 Maurin and Raoult, "Q Fever," 524–527.

813 Wagg, "Q Fever," 203.

814 R. J. Huebner, "Report of an Outbreak of Q Fever at the National Institute of Health," *American Journal of Public Health* 37 (April 1947): 431–40.

815 Denis W. Spelman, "Q Fever: A Study of 111 Consecutive Cases," *The Medical Journal of Australia* 1, no. 13 (June 26, 1982): 547–553.

816 T. J. Marrie et al., "Exposure to Parturient Cats: A Risk Factor for Acquisition of Q Fever in Maritime Canada," *The Journal of Infectious Diseases* 158, no. 1 (July 1988): 101–108.

The incubation period model given by the *P-8 BMR* was derived from a combination of the dose dependent time to onset recorded in the Tigertt studies[817] and the unpublished case studies described in the infectivity submodel section above. The equation in the *P-8 BMR* is of the form:

$$t_0 = b + m * \log(N_0)$$

where t_0 = time to onset (days), and N_0 = dose ($GPIPID_{50}$s).[818]

The *P-8 BMR* values of b and m (17.3425 days and –1.8162 days/log (dose), respectively) are based on the body temperature measurements contained in the clinical records associated with the Tigertt study subjects and the unpublished MRV cases.[819] However, neither the *P-8 BMR* nor *Consequence Analytic Tools for NBC Operations* provide the time to onset data for the unpublished MRV cases. Further, the values of b and m in the *P-8 BMR* do not yield a good fit to the data published by Tigertt and Benenson (reproduced in Table 189).

Table 189. Q Fever Observed Incubation Period Data and Predictions

$GPIPID_{50}$	Organisms	Observed Time to Onset (days)	*P-8 BMR* Predicted Time to Onset (days)	IDA Predicted Time to Onset (days)
10	20	17	16	17
10	20	17	16	17
50	100	14	14	16
50	100	17	14	16
50	100	17	14	16
150	300	12	13	15
150	300	14	13	15
150	300	15	13	15
150	300	15	13	15
150	300	16	13	15
150	300	18	13	15
1,500	3,000	13	12	13
1,500	3,000	13	12	13
1,500	3,000	14	12	13
1,500	3,000	14	12	13

817 Tigertt and Benenson, “Studies on Q Fever in Man.”

818 Anno et al., *AMedP-8* (*Biological*) *Methods Report*, 130.

819 Ibid., 129.

$GPIPID_{50}$	Organisms	Observed Time to Onset (days)	*P-8 BMR* Predicted Time to Onset (days)	IDA Predicted Time to Onset (days)
15,000	30,000	9	10	11
15,000	30,000	9	10	11
15,000	30,000	11	10	11
15,000	30,000	13	10	11
150,000	300,000	10	8	9
150,000	300,000	10	8	9

To attempt to improve the fit, we generated different values for b and m (19.6 days and–1.88 days/log (dose), respectively) based only on what was published by Tigertt and Benenson and found that our fit was superior.[820] Although this fit did not include the 13 additional patients included by the authors of the *P-8 BMR*, we know from the analysis of infectivity (Table 188) that the doses the additional patients were exposed to are within the range of doses reported by Tigertt and Benenson, so it is reasonable to expect that they would not be associated with significantly different onset times. Of course, without examining the data, it is impossible to be certain.

Until the MRV records can be reviewed, we believe it best to use the IDA model that is derived from the published Tigerrt and Benenson data lone, and have implemented the IDA model in *AMedP-7.5*.

Injury Profile

Q fever is a relatively mild, febrile illness that rarely requires hospitalization. Maurin and Raoult report that 95% of symptomatic patients will not require hospitalization.[821] Delsing speculates that only 20% of Q fever infections require medical attention and that only 2%–3% result in hospitalization.[822]

Although many individuals infected with Q fever do not become ill,[823] the method by which the *AMedP-7.5* infectivity model was derived precludes the necessity of considering the rate of asymptomatic infection—we focus on those who are symptomatic and therefore potentially casualties. In these cases, symptoms are varied and nonspecific. *MABW*

820 The onset times predicted by the *P-8 BMR* for the Tigertt dataset had an R^2 value of 0.40 when compared with the observed data; those predicted by the IDA function had an R^2 value of 0.73.

821 Maurin and Raoult, “Q Fever,” 533.

822 C. E. Delsing and B. J. Kullberg, “Q fever in the Netherlands: a concise overview and implications of the largest ongoing outbreak,” *The Netherlands Journal of Medicine* 66, no. 9 (October 2008): 365–367.

823 Maurin and Raoult, “Q Fever,” 532.

describes the most common symptoms of Q fever as fever, severe headache, and chills, with fatigue and sweats frequently found.[824] Other symptoms occasionally associated with Q fever include cough, nausea, vomiting myalgia, arthralgia, and chest pain. Pneumonia is common, particularly in cases where infection occurs through inhalation, and hepatitis is often found. Note that the rates of pneumonia and hepatitis in outbreaks of Q fever are highly variable and appear to be influenced by geography. In a study of 66 hospitalized cases of Q fever in the province of Barcelona in Spain, 37 (56%) had pneumonia and 22 (33%) had hepatitis.[825] This fits with another study in the Basque area of Spain (Valmaseda), in which 25 out of 42 patients (59.5%) had respiratory symptoms, or pneumonia, and 16 out of 42 (38.1%) had liver involvement, or hepatitis.[826] Other parts of Spain, however, appear to have different rates, since in Sevilla, in the south of Spain, 148 out of 231 patients (64%) had hepatitis while only 41 out of 231 patients (17.7%) had respiratory symptoms.[827] Since these latter were cases from a hospital, however, the severity was possibly skewed.

The variability in presentation of illness may result from differences in source, route of entry, dose, or virulence of the organism.[828] Maurin and Raoult speculate that the differences may be due to route of entry (whether aerosol or ingestion), but this is still not well understood.[829] The pneumonia is usually atypical and often only diagnosed via an X-ray, with a very low incidence of acute respiratory distress.[830] Similarly, hepatitis is usually detected through abnormal liver function tests, rather than jaundice.

Some articles give specific outlines for the course of the illness that are consistent with the idea that the illness is "moderate" on the *AMedP-7.5* Injury Severity scale (Table 2). Derrick's original characterization of the disease[831] described an acute onset with malaise, anorexia, headache, pains in the back and limbs, and feverishness. As the illness progresses, the symptoms became more severe as temperature increased, up to about 40 °C

824 Waag, "Q Fever,"203.

825 M. Sampere et al., "Q Fever in Adults: Review of 66 Cases," *European Journal of Clinical Microbiology & Infectious Diseases* 22 (2003): 108–110.

826 C. A. Errasti et al., "An Outbreak of Q Fever in the Basque Country," *The Canadian Medical Association Journal* 131 (July 1, 1984): 48–49.

827 A. de Alarcon et al., "Q Fever: Epidemiology, Clinical Features and Prognosis: A Study from 1983 to 1999 in the South of Spain," *Journal of Infection* 47 (2003): 110–116.

828 Sawyer, Fishbein, and McDade, "Q Fever: Current Concepts," 937.

829 Maurin and Raoult, "Q Fever," 528.

830 Maurin and Raoult, "Q Fever," 532.

831 E. H. Derrick, "Q Fever, a New Fever Entity: Clinical Features, Diagnosis and Laboratory Investigation," *Reviews of Infectious Diseases* 5, no. 4 (July–August 1983): 790–800.

(104 °F). Headache was persistent and often interfered with sleep. The symptoms abated as body temperature fell.

Derrick's later characterization of the illness also described the usual course of fever.[832] Typically, there would be a rapid ascent of fever for 2 to 4 days, with a plateau at about 102–104 °F (39–40 °C), sometimes broken by remissions. There would be a defervescence and an overall duration of 5 to 14 days. Twenty-eight percent of the fevers came twice. In some, the fever was high for a variable length of time, and the temperature fell gradually. Maurin and Raoult[833] describe the same course of illness, referencing Derrick. Baca and Paretsky[834] also describe a similar profile, with a febrile onset reaching a plateau of 40 °C (104 °F) within 2 to 4 days, later accompanied by malaise, anorexia, muscle pain, weakness, and intense headache. Still later, the headache became generalized and continued in intensity throughout the disease. A gradual defervescence would then occur over a 1- to 2-week period, although in older patients the fever may last longer and may display biphasic peaks.

Symptoms that were reported in more than 50% of the cases we reviewed are included in the Q fever Injury Profile, shown in Table 190. As discussed in the next section (0), it does not seem warranted to model Q fever with two stages; the Injury Profile for Q fever contains only one stage.

Table 190. Q Fever Injury Profile

	Stage 1
Signs and Symptoms (S/S)	Fever, chills, headache, myalgia, pneumonia; hepatitis
S/S Severity	2 (Moderate)

Duration of Illness

The duration of Q fever is generally cited to be from 1 to 3 weeks. *MABW* cites a duration of approximately 13 days.[835] The *P-8 BMR* cites a duration of 3 to 7 days with antibiotic given within the first 3 days of symptoms or a duration of 6 to 14 days without treatment. The *P-8 BMR* treated model was based on the Tigertt data, and the untreated model was based on the assumption that untreated cases lasted twice as long.[836] The assumption was based on two references that show that the 50% reduction in time is

832 Derrick, E.H., "The Course of Infection with *Coxiella burneti*."

833 Maurin and Raoult, "Q Fever."

834 O. G. Baca and D. Paretsky, "Q Fever and *Coxiella burnetii*: A Model for Host-Parasite Interactions," *Microbiological Reviews* 47, no. 2 (June 1983): 127–149.

835 Waag, "Q Fever," 203.

836 Anno et al., *AMedP-8* (*Biological*) *Methods Report*, 132.

specifically associated with fever, not all Q fever symptoms.[837] Although this was reasonable for the *P-8 BMR* since the methodology revolved around fever and associated performance decrements, it is not appropriate for *AMedP-7.5,* where all symptoms are considered.

Instead, we used data from 151 cases taken from two reports[838] summarizing the duration of the febrilic phase[839] in cases that occurred before antibiotics were available to derive a new duration of illness model. The data are summarized in Table 191.

Table 191. Q Fever Duration of Illness Data from Derrick or Hornibrook

Duration of Febrilic Phase	Derrick Frequency	Hornibrook Frequency
2 days	0	1
5 days	2	1
6 days	5	0
7 days	9	1
8 days	17	2
9 days	23	1
10 days	15	1
11 days	8	2
12 days	8	1
13 days	5	2
14 days	5	0
15 days	6	1
16 days	4	0
17 days	3	0
18 days	4	0
19 days	1	0
20 days	2	0
22 days	1	0
23 days	1	0

837 Spelman, "Q Fever: A Study of 111 Consecutive Cases," 551, and Sawyer, Fishbein, and McDade, "Q Fever: Current Concepts," 940.

838 Derrick, "The Course of Infection with *Coxiella burneti*;" and Hornibrook and Nelson, "An Institutional Outbreak of Pneumonitis I. Epidemiological and Clinical Studies." Hornibrook's dataset included two cases in which duration of illness was described generally as "more than five days;" we did not use these data.

839 Although there is a post-febrilic phase, it does not appear to be associated with symptoms, but rather an enduring infection that is asymptomatic until eventually cleared. Thus, the end of the febrilic phase is the relevant point in time for *AMedP-7.5*.

Duration of Febrilic Phase	Derrick Frequency	Hornibrook Frequency
24 days	1	0
25 days	1	0
26 days	3	0
27 days	2	0
28 days	2	0
29 days	3	0
30 days	2	0
31 days	1	0
33 days	1	0
43 days	1	0
57 days	1	0

Using the @RISK software,[840] the best fit to the data according to root-mean-square error was a lognormal probability distribution with a mean incubation period of 12.1 days and a standard deviation of 6.66 days (μ = 2.361; σ = 0.514).

Medical Countermeasures and Treatment Model

Because Q fever is a typically mild, self-limiting disease, medical management focuses on identifying and treating those rare cases of chronic infection that can have severe, long-term consequences. Although acute Q fever resolves spontaneously without the intervention of antibiotic therapy, uncertainty regarding the development of chronic infection makes treatment advisable.

The following subsections discuss the effects of pre-exposure vaccination and of antibiotic treatment for the symptomatic. The use of antibiotics only affects the duration of illness model; the other models are the unchanged.

Pre-Exposure and Post-Exposure Prophylaxis

The Q-Vax vaccine is licensed for use in Australia; studies have shown it to be 100% efficacious in protecting individuals in occupational settings in that country.[841] The U.S. CDC can provide the vaccine to at-risk individuals as an investigational new drug (IND). Q fever vaccination is contraindicated for individuals with prior exposure to Q fever, because severe local reactions can occur at the injection site. A skin test is available to

840 *@Risk for Excel.*

841 Waag, "Q Fever," 206.

determine a history of previous exposure.[842] There is a note under *AMedP-7.5* Table 5-60 acknowledging the fact that not all NATO nations have access to Q-Vax,

MMBC states that "chemoprophylaxis begun 8 to 12 days postexposure is effective" and that "chemoprophylaxis given within 1 to 7 days of exposure is not effective and may only prolong the onset of disease."[843] Many other sources, including the CDC,[844] repeat similar statements instructing clinicians to wait until Day 8 to begin antibiotics. This claim is apparently based on data presented by Tigertt,[845] reproduced in Table 192. There are several problems with using the Table 192 to conclude that antibiotic treatment should be delayed:

- Small number of data points in all subgroups (control, Day 1 treatment, Day 8–12 treatment);[846]
- Likelihood that a longer course of antibiotic treatment for the Day 1 treated individuals would have cleared the infection (note that treatment was only 5 to 6 days in duration, whereas current CDC recommendation is 2–3 weeks of antibiotic treatment for acute Q fever and 18 months for chronic Q fever[847]); and
- Modern availability of antibiotics to which *C. burnetii* may be more susceptible than it is to terramycin (such as doxycycline, the current CDC recommendation for treatment[848]).

842 Centers for Disease Control and Prevention, "Q Fever Prevention," last updated November 13, 2013, http://www.cdc.gov/qfever/prevention/index.html.

843 USAMRIID, *Medical Management of Biological Casualties Handbook*, 73.

844 Centers for Disease Control and Prevention (CDC), "Symptoms, Diagnosis, and Treatment," last modified November 13, 2013, http://www.cdc.gov/qfever/symptoms/index.html#treatment.

845 Tigertt, "Studies on Q Fever in Man," Table 2.

846 There are really only *four* relevant patients in each of the treatment groups: the dose, 300 organisms, is approximately the ID_{80}, so we expect four of the five individuals who began treatment on Day 1, and four of the five individuals who began treatment on days 8–12 to become ill even in the absence of any treatment. Indeed, four of five controls became ill and only four of five Day 1 treated individuals had delayed onset illness, and one patient in each group showed no evidence whatsoever of infection.

847 CDC, "Symptoms, Diagnosis, and Treatment."

848 Ibid.

Table 192. Human Response to Respiratory Challenge with 300 Organisms of *C. burnetii*

Case No.	Prophylaxis[a]	First Day of Clinical Disease	Days Organisms Isolated	Day of Initial Complement-Fixation Response
118	None	12	10–17	24
148	None	14	14	28
119	None	16	9–22	38
117	None	18	17–23	38
146	None	None	None	None
125	8	None	29	43
126	8	None	None	43
120	12	None	None	None
128	12	None	12	77
122	12	None	33–37	69
192	1	25	25	44
198	1	25	25	35
190	1	28	None	44
191	1	29	30–32	44
196	1	None	None	None

Note: "day" refers to day post-exposure.

[a] 21.0 grams of terramycin over a 5- to 6-day period.

A proper investigation of whether it is wise to delay antibiotic treatment for *C. burnetii* exposure, which would require considering the significant amount of research that has been conducted on the organism and disease in the last few decades, is beyond the scope of this document.

We also believe it unwise to use the Table 192 data to attempt to determine the efficacy of prophylaxis. There are simply too few subjects to have any statistical confidence in a model derived from the data. Thus, although it is likely that post-exposure antibiotic prophylaxis would be prescribed following suspected exposure to *C. burnetii*, and would prevent illness to some extent, *AMedP-7.5* does not include a model to incorporate the effects of such prophylaxis.

c. Duration of Illness

While comparative studies of the efficacy of antibiotics are scarce, there is some evidence that a course of antibiotics begun within a few days of onset can reduce the duration of fever. Other symptoms, such as lethargy, sweats, and headache, have been found to persist despite antibiotic treatment, and the relationship between antibiotic use and the overall duration of illness is not described in the literature.

In a study of 111 cases of Q fever in Australia, the average fever duration in untreated cases was 3.3 days, while the average duration for patients treated with tetracycline was 2 days, and average duration for patients treated with doxycycline was 1.7 days.[849]

In the studies conducted by Tigertt and colleagues, individuals who developed symptomatic disease were given oral tetracycline within 24 hours of the onset of persistent fever. In these experiments, infection responded promptly to treatment with antibiotics, with a cessation of symptoms within 24 to 48 hours.[850]

To be on the conservative side while we wait to analyze the MRV clinical records, and considering that the currently recommended course of antibiotics lasts for 14 days,[851] the *AMedP-7.5* model for the duration of illness in treated Q fever patients is a fixed time of 5 days from the initiation of antibiotic therapy to the time an individual is eligible to RTD.

Model Summary

Table 193 and Table 194 summarize the model parameters for Q fever used in *AMedP-7.5*. If the opportunity to review unpublished records from the MRVs arises, it may be possible to refine some of the models, but it is not expected that a significant change to the models would be necessary, since they are already based on human cases.

Table 193. Q Fever Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 30 organisms Probit slope = 0.782 probits/log (dose)
• Pre-exposure vaccination	Rate (efficacy)	100%
Lethality	Rate	0%
Incubation period	Log-linear function	m = -1.88 days/log (dose) b = 19.6 days
Duration of illness		
• Stage 1 (untreated)	Lognormal distribution	Mean = 12.1 days Standard deviation = 6.66 days μ = 2.361; σ = 0.514
• Total duration after initiation of antibiotics (treated survivors)	Constant	5 days

Table 194. Q Fever Injury Profile

	Stage 1

849 Spelman, "Q Fever: A Study of 111 Consecutive Cases," 551

850 Tigertt, "Studies on Q Fever in Man," 100.

851 Maurin and Raoult, "Q Fever"; Waag, "Q Fever."

Signs and Symptoms (S/S)	Fever, chills, headache, myalgia, pneumonia; hepatitis
S/S Severity	2 (Moderate)

Cohorts and Special Considerations (*AMedP-7.5 Section 5.2.7.3*)

The definitions of the cohorts are sufficiently explained in *AMedP-7.5*. This section explains the equations used to calculate the cohort populations; for definitions of the variables in the equations, see *AMedP-7.5*.

Equation 5-63:	Those who have already recovered from the illness and become eligible for RTD before treatment was initiated
Equation 5-64:	Anyone who has not yet completed incubation
Equation 5-65:	Those who have completed incubation, minus those who have also already recovered and become eligible for RTD (to avoid double counting)

1.25. Tularemia Model
(*AMedP-7.5 Section 5.2.8*)

Introduction

Tularemia is a zoonosis caused by the bacterium *Francisella tularensis*. Endemic to North America and Eurasia, tularemia was first investigated by researchers from the U.S. Public Health Service, including McCoy and Chapin, who in 1911 first isolated the bacteria from infected ground squirrels in Tulare County, California,[852] and Edward Francis, who pioneered research of the disease in humans.[853] The bacteria has four identified subspecies; Type A (tularensis) occurs predominantly in North America and is the most virulent subspecies in both animals and humans.[854] After tularemia was identified, diagnosis of the disease increased dramatically, with the incidence of reported cases of tularemia in the United States peaking at about 2,300 in 1939. Today, tularemia is rare in the United States, with only about 100 cases reported per year.[855]

Humans can acquire tularemia in a variety of ways: direct contact with infected animals or their tissues, ingestion of infected meat or contaminated water, animal bites or scratches, insect bites, and inhalation of contaminated aerosols.[856] Small mammals, such as rabbits, hares, voles, mice, rats, and squirrels, are the natural reservoirs of infection, and they acquire tularemia via insect bites or contact with contaminated environments.[857]

Tularemia has a variety of clinical manifestations, depending to some extent on the route of infection (although symptoms overlap). The onset is typically abrupt, with a high fever, headache, chills and rigors, body aches, runny nose, and sore throat.[858] Francis described two types of infection:[859] glandular (or ulceroglandular), with enlarged glands and an evident local site of infection, and typhoidal, with symptoms similar to those

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852 G. W. McCoy and C. W. Chapin, "Further Observations on a Plaguelike Disease of Rodents with a Preliminary Note on the Causative Agent *Bacterium tularense*," *Journal of Infectious Diseases* 10 (1912): 61–72.

853 Edward Francis, "Tularemia," *The Journal of the American Medical Association* 84, no. 7 (1925): 1243–1250.

854 Matthew J. Hepburn, Arthur M. Friedlander, and Zygmunt F. Dembek, "Tularemia," chap. 8 in *Medical Aspects of Biological Warfare*, ed. Zygmunt F. Dembek, *Textbook of Military Medicine* (Washington, DC: Department of Defense, Office of the Surgeon General, U.S. Army, Borden Institute, 2007), 168.

855 Richard Hornick, "Tularemia Revisited," *New England Journal of Medicine* 345, no. 22 (2001): 1638.

856 Hepburn, Friedlander, and Dembek, "Tularemia," 169.

857 David T. Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," *Journal of the American Medical Association* 285, no. 21 (2001): 2764.

858 Ibid., 2767.

859 Francis, "Tularemia," 1246–1247.

associated with typhoid fever and without enlarged glands or observable local site of infection. This taxonomy was commonly used in published clinical studies of tularemia cases throughout the period of greatest incidence, but currently a more specific categorization is preferred.[860] Disease manifestations of tularemia are now generally divided into seven categories:[861]

- Ulceroglandular, characterized by a persistent ulcer at the site of infection combined with painful enlarged lymph nodes;
- Oculoglandular, similar to ulceroglandular but with the eye as the site of infection;
- Glandular, characterized by painful enlarged lymph nodes but without a cutaneous ulcer;
- Oropharyngeal, characterized by soreness and irritation of the throat and thought to be caused by ingestion of contaminated food or water;
- Pneumonic, characterized by pulmonary signs and symptoms consistent with pneumonia;
- Typhoidal, which presents as a nonspecific febrile syndrome; and
- Septic, which is the result of clinical progression of any other form of tularemia to a state of septic shock.

The pneumonic form of tularemia can occur directly from the inhalation of contaminated aerosols, or secondarily via the spread of the bacteria to the lungs from other parts of the body. Because exposure to biological warfare agents typically occurs via inhalation, the *AMedP-7.5* model of tularemia focuses on the pneumonic form.

Assumption and Limitation (*AMedP-7.5 Section 5.2.8.2*)

Assumption: Inhalation of *F. tularensis* results in typhoidal tularemia with pneumonia.

See Subsection 0 for explanation (particularly the last two paragraphs).

Limitation: Although the model requires the user to specify a day on which antibiotic treatment becomes available ($d_{trt\text{-}tul}$), it does *not* apply treatment to every person on that day; only those who have been declared WIA are modeled to begin receiving antibiotics on that day. Those who are declared

860 Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," 2767.

861 Hepburn, Friedlander, and Dembek, "Tularemia,"172–173.

WIA after $d_{trt\text{-}tul}$ are modeled to begin receiving antibiotics on the day they are declared WIA.

Although this is stated as a limitation, it is actually the most sensible way to apply treatment.

Human Response Model (*AMedP-7.5 Tables 5-67 to 5-69*)

Literature Summary

Important source documents for the tularemia model include the relevant *MABW* chapter[862] and the *JAMA Consensus Statement on Tularemia*[863]—both of which are extensively referenced literature reviews conducted by groups of subject-matter experts selected by the sponsoring organizations (the U.S. Army and the American Medical Association (AMA))—the *P-8 BMR*, and *Consequence Analytic Tools for NBC Operations*. These documents were used to identify authoritative sources of data for use in populating various submodels, including primary source data where possible. Although the last two sources overlap greatly in their presentation of model parameters, *Consequence Analytic Tools for NBC Operations* contains some unique information and a fuller discussion of the underlying analysis; hence it is the document referenced in this study's discussion of tularemia submodel parameters.

The models in the *P-8 BMR* and *Consequence Analytic Tools for NBC Operations* are derived from experimental data recorded during human testing of a tularemia vaccine with MRVs. Much of the MRV data remain unpublished, and IDA researchers have not yet been able to analyze them.

The basis of the *AMedP-7.5* models—the untreated models—describe the progression of illness in the absence of treatment. Today, tularemia is readily cured by the administration of antibiotics, and modern clinical studies of the illness assume treatment. We therefore relied on data published before the advent of routine antibiotic use for the characterization of mortality, Injury Profile, and duration of illness. While the incidence of tularemia in the United States peaked in this period and relevant data are prevalent, there are some difficulties associated with adapting this information for use in the model. Specifically, some of the most comprehensive clinical studies of tularemia were conducted when Francis' taxonomy of tularemia infections (glandular and typhoidal) was generally used and before inhalation was understood to be a potential route of infection.

Patients with typhoidal tularemia were much more likely to develop pneumonia, at a rate of approximately 50%, versus those with ulceroglandular tularemia, only 12% to 15%

862 Hepburn, Friedlander, and Dembek, "Tularemia."

863 Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management."

of whom developed pneumonia.[864] The similarities in clinical manifestation of disease in typhoidal tularemia patients with pneumonia and in patients subjected to aerosol challenge vaccine studies suggested that at least some typhoidal tularemia patients had acquired the disease via inhalation, although this point of view was somewhat controversial.[865]

While the route of exposure for typhoidal patients both with and without pneumonia remains a matter of speculation, we believe that historical data on typhoidal tularemia patients with pneumonia provide the best available data to characterize mortality, Injury Profile, and duration of illness for the tularemia human response model.

Infectivity

Both *MABW* and the *JAMA Consensus Statement on Tularemia* note that tularemia is remarkable for its low infectious dose—on the order of 10 organisms from either the cutaneous or the inhalation route of entry. Both cite the two published tularemia vaccine studies involving human volunteer subjects by Saslaw et al., the first of which describes intracutaneous challenge[866] and the second of which describes respiratory challenge.[867]

Saslaw reported on 20 unvaccinated controls that were exposed to 10 to 52 organisms via inhalation; of these, 16 became ill. However, *Consequence Analytic Tools for NBC Operations* reports an additional 96 cases with higher challenge doses (ranging from 315 to 62,000 organisms); in all cases the MRVs became ill.[868] However, *Consequence Analytic Tools for NBC Operations* does not provide individual dose data for the 96 cases with higher challenge. It does, however, provide dose-response data for two other cases not included in Saslaw's report: exposures of 10 and 17 organisms, both of which failed to induce illness.[869]

Although we have been unable to analyze the MRV records to determine for ourselves the preferred dataset to use for estimating the infectivity of *F. tularensis*, we thought it best to include the two additional cases not reported by Saslaw. Thus, Table 195 summarizes the data published by Saslaw and the two additional cases reported in *Consequence*

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864 Fred McCrumb, Jr., "Aerosol Infection of Man with *Pasteurella Tularensis*," *Bacteriological Review* 25 (1961): 262.

865 Ibid. As McCrumb states: "It should be recognized that the mechanism of infection in so-called typhoidal tularemia is still a matter of controversy, there being those who doubt the importance or even the existence of primary pneumonic tularemia. One of the objectives of this presentation will be to marshal evidence in support of the concept that primary respiratory tularemia occurs as a naturally acquired as well as induced disease."

866 Samuel Saslaw et al., "Tularemia Vaccine Study, I: Intracutaneous Challenge," *Archives of Internal Medicine 107* (1961): 121–133.

867 Samuel Saslaw et al., "Tularemia Vaccine Study, II: Respiratory Challenge," *Archives of Internal Medicine 107* (1961): 134–146.

868 Anno et al., *Consequence Analytic Tools for NBC Operations*, 17–19, 25.

869 Anno et al., *Consequence Analytic Tools for NBC Operations*, 17.

Analytic Tools for NBC Operations. Probit analysis on these data produces an ID_{50} of 10 organisms and probit slope of 1.90 probits/log (dose).

Table 195. Tularemia Respiratory Challenge Data

Individual Dose (organisms)	Became Symptomatic?
10	No
10	No
10	Yes
12	No
14	Yes
15	Yes
16	Yes
17	No
18	Yes
18	Yes
20	No
20	Yes
23	Yes
23	Yes
25	Yes
30	Yes
45	No
46	Yes
46	Yes
48	Yes
50	Yes
52	Yes

Source: Saslaw et al., "Tularemia Vaccine Study, II: Respiratory Challenge," 137, 140; Anno et al., *Consequence Analytic Tools for NBC Operations*, 17.

Lethality

Today tularemia is readily treated with antibiotics, and deaths from the disease are extremely rare. Before antibiotic use, however, lethality was high. *MABW* provides a range of 5% to 57%, depending on type of infection,[870] while the *JAMA Consensus Statement on*

870 Hepburn, Friedlander, and Dembek, "Tularemia," 168.

Tularemia reports that mortality rates were in the range of 5% to 15% overall, but 30% to 60% for pneumonic and severe systemic forms of the disease.[871]

The *P-8 BMR* states that the mortality rate for untreated pneumonic treatment is 30% to 40%,[872] citing *Consequence Analytic Tools for NBC Operations*, which in turn references personal communications from subject-matter experts for this value.[873] The *P-8 BMR* combines a postulated constant daily lethality rate with a dose-dependent duration of fever model to result in a dose-dependent model of lethality. By assigning a value of 3% to the daily lethality rate, the *P-8 BMR* was able to generate an overall lethality rate of 20% to 50%, depending on dose.[874]

Both *MABW* and the *JAMA Consensus Statement on Tularemia* cite a 1945 study by Stuart and Pullen[875] in which the authors reviewed available literature on pneumonic tularemia and reported on additional pneumonic cases they had personally managed at Charity Hospital in New Orleans, Louisiana. These same authors separately published an analysis of 225 tularemia cases of all types seen at Charity Hospital from 1928 through 1944.[876]

Of the 225 cases of tularemia observed by Stuart and Pullen, only 14 were of the typhoidal form (about 6% overall); the remainder were ulceroglandular (80%), oculoglandular (3%), and glandular (10%). There were 17 deaths among these cases, for an overall lethality rate of about 8%. The lethality rate varied by type of infection, however: the rate among typhoidal patients was 50%, while the rate among all other types of tularemia infection was less than 5%. Of those who died, 15 of 17 had pneumonia listed as a presumptive cause of death.[877]

Stuart and Pullen's literature review considered 268 cases of pneumonic tularemia resulting in 107 deaths, a lethality rate of 40%.[878] These cases include pneumonias that

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871 Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," 2767.

872 Anno et al., *AMedP-8* (*Biological*) *Methods Report*, 80.

873 Anno et al., *Consequence Analytic Tools for NBC Operations*, 16. This document footnotes additional sources describing lethality rates as high as 60% for tularemia in its more severe forms. See for example L. Foshay, "Diagnosis and Treatment of Tularemia," *Postgraduate Medicine* 4, No. 4 (October 1948).

874 Anno et al., *AMedP-8* (*Biological*) *Methods Report*, 78–80.

875 Byron M. Stuart and Roscoe L. Pullen, "Tularemic Pneumonia: Review of American Literature and Report of 15 Additional Cases," *American Journal of Medical Science* 210 (1945): 223–36.

876 Roscoe L. Pullen and Byron M. Stuart, "Tularemia: Analysis of 225 Cases," *Journal of the American Medical Association* 129 no. 7 (1945): 495–500.

877 Ibid., 500.

878 Stuart and Pullen, "Tularemic Pneumonia," 231.

developed among tularemia cases of all types; for those reported in the literature, Stuart and Pullen did not categorize lethality rates by type of tularemia. However, they noted that in their literature review, the reported symptoms of patients with pneumonic tularemia fell into two general groups, with those experienced by typhoidal patients being distinctly different than those experienced by patients with ulceroglandular, glandular, or oculoglandular tularemia.[879]

The Stuart and Pullen study provides data on type of tularemia for the 21 cases of pneumonia among tularemia patients they personally observed at Charity Hospital; among these, there were 12 deaths, for an overall lethality rate of 57% among pneumonic cases of tularemia.[880] All these cases were either of the ulceroglandular or typhoidal forms; lethality rates were 46% for ulceroglandular patients (6 of 13) and 75% for typhoidal patients (6 of 8).

Consistent with the above, the literature in general suggests that among historical cases, lethality rates were higher for typhoidal tularemia patients than for patients with other forms of tularemia (around 50%) and for tularemia patients of all forms who developed pneumonia (around 40%). Stuart and Pullen do not describe the extent of overlap in these categories among reported cases, but in the cases they observed that were both pneumonic and typhoidal, the lethality rate was significantly higher, at 75%. Because we believe that data from historical cases of typhoidal tularemia with pneumonia provide the best surrogate data for untreated tularemia acquired via inhalation, the *AMedP-7.5* lethality model for tularemia is a CFR of 75%, as observed in the Stuart and Pullen study.

Incubation Period

The incubation period for pneumonic tularemia acquired via inhalation is rarely discussed in clinical studies of the disease. Unless the exposure is controlled, as in the case of the vaccine challenge studies, or is the result of a laboratory accident, it is difficult to know exactly when exposure occurred. The *JAMA Consensus Statement on Tularemia*

879 Ibid., 227.

880 Three of the deaths reported by Stuart and Pullen (Pullen and Stuart, "Tularemia: Analysis of 225 Cases") listing pneumonia as a presumptive cause of death were excluded from the reported pneumonic cases (Stuart and Pullen, "Tularemic Pneumonia") because they did not meet their criteria for diagnosis of tularemia. These criteria included (1) autopsy with recovery of the organism from culture or animal inoculation; (2) aspiration biopsy of the lung with recovery of the organism from culture or animal inoculation; and (3) positive physical signs of pneumonic consolidation with X-ray confirmation and rising blood agglutination titers for the organism (Stuart and Pullen, "Tularemic Pneumonia," 232). None of the excluded cases was typhoidal.

states, without attribution, that the incubation period for tularemia acquired via inhalation ranges from 1 to 14 days, with most cases occurring 3 to 5 days after exposure.[881]

Using the unpublished MRV case data, the authors of *Consequence Analytic Tools for NBC Operations* found that incubation period correlates with challenge dose. They derived the relationship between the logarithm of dose and incubation period using a regression model of the form:

$$t_0(N_0) = b + m \log N_0,$$

where:

t_0 = time to onset of infection (days),

N_0 = dose (organisms inhaled),

b = 6.5380 days, and

m = –0.8207 days/log (dose).[882]

Extrapolation to a single organism results in an onset time of about 6.5 days. In consultation with subject-matter experts, *Consequence Analytic Tools for NBC Operations* also established a minimum onset time of 1.5 days in cases of very high doses (those in excess of 10^7 organisms).[883] For doses in the range of 10^5 to 10^7 organisms, the authors proposed a logarithmic/quadratic relationship of the following form:

$$t_0(N_0) = c + b \log N_0 + a (\log N_0)^2,$$

where:

t_0 = time to onset of infection (days),

N_0 = dose (organisms inhaled),

c = 10.9563 days,

b = –2.5886 days/log (dose) and

a = 0.1763 days/(log (dose))^2.[884]

881 Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," 2765.

882 Anno et al., *Consequence Analytic Tools for NBC Operations*, 28–29.

883 Ibid., 30.

884 Ibid., 31.

Thus in the model described in *Consequence Analytic Tools for NBC Operations*, the range of onset times for tularemia is bounded at 1.5 and 6.5 days.

As noted, the dataset used in *Consequence Analytic Tools for NBC Operations* included the 16 cases of positive response described in the Saslaw vaccine respiratory challenge study as well as 96 other cases described in the set of unpublished MRV data. These latter cases were all exposed to higher challenge doses than those in the Saslaw study, ranging from 315 to 62,000 organisms.

The published Saslaw data includes values for incubation periods for positive responses. Table 196 provides dose and observed incubation period from the Saslaw study and an incubation-period estimate from the model in *Consequence Analytic Tools for NBC Operations*. As can be seen from the table, there is indeed a tendency for incubation period to be shorter given a higher dose. Although the range of observed incubation periods is greater than that seen in the predicted incubation period, we found the results of the *Consequence Analytic Tools for NBC Operations* model to be reasonable: the Saslaw dataset is small relative to that used in *Consequence Analytic Tools for NBC Operations*, and the small challenge doses likely fall in the tail of the distribution, where greater variance would be expected. Therefore, *AMedP-7.5* implements the model from *Consequence Analytic Tools for NBC Operations* in its Tables 5-66 through 5-70 (the effects of the dose-dependent model also propagate into *AMedP-7.5* Tables 5-71 through 5-76).

Table 196. Tularemia Incubation Period Data from Saslaw and *Consequence Analytic Tools for NBC Operations* Predicted Values

Individual Dose (organisms)	Observed Incubation Period (days)	Consequence Analytic Tools for NBC Operations Predicted Incubation Period (days)
10	6	5.7
14	5	5.6
15	6	5.6
16	6	5.5
18	5	5.5
18	7	5.5
20	7	5.5
23	6	5.4
23	6	5.4
25	5	5.4
30	5	5.3
46	4	5.2

46	4	5.2
48	5	5.2
50	4	5.1
52	5	5.1

Source: Saslaw et al., "Tularemia Vaccine Study, II: Respiratory Challenge," 137, 140.

Injury Profile

Tularemia initially presents as a sudden, acute, nonspecific febrile illness, and it is very difficult to diagnose if not of the ulceroglandular or oculoglandular forms. Even in its initial stage, the disease is generally severe; the *JAMA Consensus Statement on Tularemia* notes that many of the MRVs exposed to aerosol challenge were incapacitated in the first 1 or 2 days of illness.[885] Recovery from tularemia is generally described as slow. As *MABW* states, "untreated tularemia patients usually have a prolonged illness lasting for months."[886] Francis observed that convalescence typically took several weeks—in rare cases as long as a year—during which time patients were extremely weak and had limited endurance.[887]

In the Saslaw study, control subjects who had a positive response to respiratory challenge experienced fever, myalgia, headache, anorexia, and dry, nonproductive cough. Substernal tightness and pain were common, and chills were occasionally observed.[888] Subjects were given antibiotics within a day or two of symptom onset and all recovered quickly; none showed pulmonary abnormalities on X-rays before therapy began.

McCrumb described the initial clinical signs and symptoms observed among eight vaccine study control subjects exposed to respiratory challenges of 200 to 20,000 organisms:[889] all controls developed disease characterized by abrupt onset of fever, headache, chills and sore throat, accompanied by malaise, myalgia and backache. Fevers were very high, fron 103 °F to 104 °F. All patients also had cough, and most experienced chest pain, either sharp pleural pain aggravated by breathing or oppressive substernal pain. X-rays showed a small, discrete pulmonary lesion in two patients.

Stuart and Pullen identified a distinct clinical presentation in typhoidal tularemia patients with pneumonia.[890] They observed sudden onset of fever, chills, shortness of

885 Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," 2767.

886 Hepburn, Friedlander, and Dembek, "Tularemia," 173.

887 Francis, "Tularemia," 1247.

888 Saslaw et al., "Tularemia Vaccine Study, II: Respiratory Challenge," 713.

889 McCrumb, "Aerosol Infection of Man with *Pasteurella Tularensis*," 264. The McCrumb article does not provide the type of dose, response, and time of onset data included in the Saslaw study, although Anno et al. include the McCrumb data in the set of unpublished MRV data they used in the development of their model.

890 Stuart and Pullen, "Tularemic Pneumonia," 227.

breath, cough, chest pain, and profuse sweating. Patients appeared extremely ill and were frequently suspected of having typhoid fever. They also observed that pulmonary symptoms were less severe than those associated with other forms of pneumonia, and symptoms of bronchitis were usually present before pneumonia was recognized. Once pneumonia manifests, it can rapidly become severe, leading to respiratory failure and death. In severe cases, Stuart and Pullen observed elevated pulse, rapid and shallow breathing, confusion, delirium, and even coma.

The Injury Profile submodel characterizes disease by the stages of its clinical course, the signs and symptoms present within each stage, and the overall severity of illness, using the scale described in Table 2. The Injury Profile comprises three stages, two for both survivors and non-survivors, and a third for survivors representing the recovery period.

Stage 1 of pneumonic tularemia encompasses the initial febrile period of the disease, marked by high fever, headache, chills, sore throat, myalgia, and chest pain. Onset is sudden, and patients in this phase of the disease appear severely ill and can be incapacitated. Consequently, this stage is characterized as Injury Severity Level 3.

Stage 2 of pneumonic tularemia begins with the onset of pneumonia. Signs and symptoms from Stage 1 continue, with the addition of respiratory distress. Non-survivors would experience respiratory distress and ultimately respiratory failure in this stage, which would end in death. The pulmonary symptoms experienced by survivors would be milder in this stage than for non-survivors, and the stage would end with the resolution of pneumonia. For non-survivors, Stage 2 is characterized as Injury Severity Level 4, while Stage 2 for survivors is characterized as Injury Severity Level 3.

Stage 3 of pneumonic tularemia is considered for survivors only and is used to represent recovery from the disease. Convalescence is protracted and is marked by severe weakness. Because patients would not be expected to resume normal activity in this period, it is characterized as Injury Severity Level 2.

Table 197 summarizes the proposed Injury Profile for pneumonic tularemia.

Table 197. Tularemia Injury Profile

	Stage 1 (all)	Stage 2 (non-survivors)	Stage 2 (survivors)	Stage 3 (survivors)
Signs and symptoms (S/S)	High fever, headache, chills, sore throat, myalgia, chest pain	Stage 1 S/S plus severe pneumonia, respiratory distress	Stage 1 S/S plus mild pneumonia	Malaise, severe weakness
S/S Severity	3 (Severe)	4 (Very Severe)	3 (Severe)	2 (Moderate)

Duration of Illness

Today, tularemia is readily treated with antibiotics. In the tularemia vaccine challenge studies conducted with human volunteers, for example, all subjects who developed disease were administered antibiotics, and in all cases the progression of disease was arrested. Development of the duration of illness submodel for tularemia must therefore rely on data from historical cases of tularemia before the antibiotic era. Once again, preference is given to data on cases of typhoidal tularemia with pneumonia.

MABW states, "untreated tularemia patients usually have a prolonged illness lasting for months,"[891] and the *JAMA Consensus Statement on Tularemia* notes that in untreated tularemia, "symptoms often persist for several weeks and, sometimes, for months, usually with progressive debility."[892] Neither reference differentiates among clinical form of the disease or provides any greater detail than that cited.

In *Consequence Analytic Tools for NBC Operations*, the authors used two historical cases of tularemia for which body temperature was recorded[893] as the basis for developing a dose-dependent duration of illness model. In one case, the febrile period lasted for 16 days; in the second, it lasted for 23 days. The authors further postulated that because the first case was significantly less severe and of shorter duration than the second, these two cases could be used as a "reasonable paradigm for high and low dose response."[894] Using the recorded temperature data for the two cases and a linear function developed from MRV data to describe time to near-maximum body temperature,[895] the authors calculated estimated doses for the first case of 10 organisms and for the second case of 44,063 organisms.[896] These estimated doses and durations of fever were then used to derive a model of duration of fever as a function of dose; this model was then qualified by limiting the febrile period to 30 days, as a result of consultation with subject-matter-experts.

The authors of *Consequence Analytic Tools for NBC Operations* were limited in their choice of historical case data on which to base their calculations by their focus on fever and its relationship to performance and the corresponding value of case records that

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891 Hepburn, Friedlander, and Dembek, "Tularemia," 173.

892 Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," 2767.

893 W. A. Simpson, *Tularemia History, Pathology, Diagnosis, and Treatment* (New York, NY: Paul B. Hoeber, Inc., 1929), referenced in Anno et al., *Consequence Analytic Tools for NBC Operations*, 33.

894 Anno et al., *Consequence Analytic Tools for NBC Operations*, 33.

895 This linear function is of the same form and developed from the same set of MRV data as that used to describe incubation period in *Consequence Analytic Tools for NBC Operations*.

896 Anno et al., *Consequence Analytic Tools for NBC Operations*, Table 2–3.

described body temperature measurements over time. For *AMedP-7.5*, such restrictions and incentives do not exist, allowing use of a broader set of case data.

Stuart and Pullen's clinical study of pneumonic tularemia patients at Charity Hospital described the duration of illness before and after pneumonia was confirmed via chest X-rays. Table 198 summarizes the information on typhoidal patients provided in that study. Although the numbers of cases are small for both survivors and non-survivors, among them the survivors had a clearly different duration of illness, particularly in the duration of pneumonia. We used these data to assign duration to various stages of illness described in the pneumonic tularemia Injury Profile. Because the numbers of cases were so small, however, no attempt has been made to derive a model in any functional form from the data; rather, we used the average values to populate the duration submodel.

Table 198. Duration of Illness Data for Typhoidal Tularemia Patients with Pneumonia

Case	Duration of Symptoms Before Pneumonia (days)	Duration of Pneumonia (days)	Total Duration of Illness (days)
Survivors #1	14	33	47
Survivors #	10	22	32
Survivor Average	***12***	***28***	***40***
Fatality #1	10	5	15
Fatality #2	6	4	15
Fatality #3	8	2	10
Fatality #4	8	2	10
Fatality #5	12	5	10
Fatality #6	9	19	17
Fatality Average	***9***	***6***	***15***

Source: Stuart and Pullen, "Tularemic Pneumonia," 233.

For the period of convalescence described by Stage 3 of the survivor Injury Profile, described in various sources as "prolonged" and "weeks to months," we arbitrarily chose a constant value of 12 weeks, or 84 days.

Medical Countermeasures and Treatment Model

Despite the history of a vaccine being available, there is currently no vaccine available for use for the prevention of tularemia. Antibiotics are effective as post-exposure prophylaxis and as treatment for the symptomatic. The following subsections discuss the historical vaccine, ongoing vaccine work (briefly), and the effects of antibiotics as both post-exposure prophylaxis and as treatment. Antibiotics as treatment affect the lethality and duration of illness models; the other models are unchanged.

Post-Exposure Prophylaxis

Coincident with work on tularemia in the offensive biological weapons program, researchers sought to develop a vaccine against the disease. The most successful of these efforts followed the isolation of the live vaccine strain (LVS) of tularemia in Russia in the 1950s and its transfer to the United States. The strain was tested as a live vaccine in MRVs in the 1950s and approved as an IND by the FDA in the 1960s.[897] The LVS vaccine has since been administered to hundreds of researchers at USAMRIID and is thought to have reduced the incidence of laboratory acquired tularemia.[898] Because it is live, the LVS can cause disease when administered in quantities required to confer immunity; as a consequence of this and other issues, the FDA has removed it from its IND list and the vaccine is currently not licensed for use.[899] Since we are unaware of any other tularemia vaccine available in NATO nations, *AMedP-7.5* does not include vaccination.

With renewed interest in tularemia as an agent of bioterrorism, including its designation by the CDC as a Category A agent, significant advances in the study of the organism's genetics and pathogenesis have recently been made.[900] These advances underlie ongoing efforts to develop a safe and effective vaccine.[901] Thus, for the next version of *AMedP-7.5*, it will be necessary to determine whether sufficient progress has been made such that a pre-exposure vaccination model should be included.

In cases where post-exposure prophylaxis could be implemented in time to prevent illness, the administration of antibiotics in a population at risk is recommended. A 1966 study of MRVs assessed the effectiveness of antibiotics in preventing the onset of disease following exposure to *F. tularensis* via inhalation.[902] In this study, 34 subjects were exposed to a respiratory challenge of 25,000 organisms and given tetracycline as a prophylaxis, in varying doses and for varying periods of time. Table 199[903] provides information on the antibiotic regimens tested in the study and their outcome.

Table 199. Tetracycline Prophylaxis of Human Airborne Tularemia

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897 Roger D. Pechous, Travis R. McCarthy, and Thomas C. Zahrt, "Working toward the Future: Insights into *Francisella Tularensis* Pathogenesis and Vaccine Development," *Microbiology and Molecular Biology Reviews* 73, no. 4 (2009): 702.

898 Hepburn, Friedlander, and Dembek, "Tularemia," 176–77.

899 Pechous, McCarthy, and Zahrt, "*Francisella Tularensis* Pathogenesis," 702.

900 Ibid., 706.

901 Hepburn, Friedlander, and Dembek, "Tularemia," 177.

902 William D. Sawyer et al., "Antibiotic Prophylaxis and Therapy of Airborne Tularemia," *Bacteriological Reviews* 30, no. 3 (1966).

903 Ibid., 545. This table—including the title and the data contained within—is a replica of the one provided in the study.

Daily Dose[a] (g)	Frequency	Duration (days)	# of Subjects	# Ill During Prophylaxis	# Ill After Prophylaxis
1	Daily	15	10	0	2
1	Daily	28	8	0	0
2	Daily	14	8	0	0
1	Every 2nd Day	19	8	2	8

[a] Divided into morning and evening doses

All subjects who developed the disease during or after the period of prophylaxis were subsequently treated with streptomycin; all recovered quickly and without complications.

The study concluded that antibiotics could successfully be used to prevent onset of illness following respiratory challenge with tularemia, provided they were administered in sufficient amounts to suppress growth of intracellular organisms, and provided they were administered for a sufficient period of time.[904] Current recommendations for dose and duration of post-exposure antibiotic prophylaxis for tularemia are derived from this study.[905]

From these data, we assume that post-exposure antibiotic prophylaxis, if continued for the recommended 14-day duration, will be completely protective against the onset of disease, with an efficacy of 100%.

Lethality

Antibiotic therapy is very effective in treating tularemia, with the overall case-fatality rate for reported cases of tularemia of all types reported in the United States currently less than 2%.[906] In the course of a number of controlled experiments in the 1950s and 1960s, hundreds of MRVs were exposed to tularemia via inhalation; all were treated with antibiotics and all survived. For example, clinical records for 118 human control subjects in three separate vaccine efficacy studies were used to develop the febrile performance model for tularemia used to generate earlier versions of *AMedP-8*; all these subjects were successfully treated with antibiotics.[907]

Because no fatalities occurred among MRVs involved in tularemia experiments, and because the mortality rates are so low among naturally occurring cases treated with

[904] Ibid., 547.
[905] Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," 2767.
[906] Dennis et al., "Tularemia as a Biological Weapon: Medical and Public Health Management," 2767.
[907] Anno et al., *Consequence Analytic Tools for NBC Operations*, 25.

antibiotics, *AMedP-7.5* considers treatment to be completely effective in preventing death from tularemia.

Injury Profile

Any person receiving antibiotics as treatment will have first entered Stage 1 of disease. Thus, the Injury Severity Level associated with Stage 1 should not be changed. Although antibiotics do lessen the later symptoms,[908] the way that *AMedP-7.5* implements the tularemia treated duration of illness model is such that changes in Injury Severity Level after the antibiotic treatment begins cannot be tracked.

d. Duration of Illness

The duration of illness submodel for tularemia with treatment is derived from the controlled human experiments described above. Unfortunately, the clinical records from these studies are not currently available, and published studies generally provide only summary statistics.

In the Alluisi study of performance degradation in tularemia and sandfly fever patients, all 16 tularemia patients developed clinical manifestations of illness 2 to 4 days after exposure. Their temperatures peaked 2 days after onset of illness and returned to normal 2 days later. One week after onset of illness, performance had recovered to 95% of baseline capability.[909]

In the Saslaw vaccine study, from which the infectivity model of tularemia is derived, some 20 control subjects developed tularemia following aerosol exposure. Overall, "therapy with 2 gm daily for 10 days of either streptomycin or tetracycline resulted in prompt amelioration of symptoms with no subsequent relapses."[910] The clinical records included in this study for illustrative purposes showed that patients were typically asymptomatic within 2 to 3 days after antibiotic therapy was initiated.

Finally, in the collection of 118 separate MRV records reviewed by Anno et al. in the development of earlier versions of *AMedP-8*, all patients were effectively treated with either streptomycin or tetracycline. In these cases, body temperature subsided to normal levels 1 to 2 days after the antibiotic was administered, and other signs and symptoms disappeared.[911]

The published data are not sufficiently complete or detailed enough to support developing a probabilistic distribution of duration of illness in treated cases. Thus, we

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908 Earl A. Alluisi et al., "Behavioral Effects of Tularemia and Sandfly Fever in Man," *Journal of Infectious Diseases* 128, no. 6 (1973): 710–717.

909 Ibid., 714.

910 Saslaw et al., "Tularemia Vaccine Study, II: Respiratory Challenge," 145.

911 Anno et al., *Consequence Analytic Tools for NBC Operations*, 25.

assumed for the *AMedP-7.5* model that the total duration of illness for tularemia is 10 days, or equal to the recommended course of antibiotic therapy.

Model Summary

Table 200 and Table 201 summarize the model parameters for tularemia used in *AMedP-7.5*. The model was derived from a collection of articles that include analyses of controlled human exposures to tularemia and analyses of cases and outbreaks. The controlled human exposure data, however, were never completely published, leading to some inconsistencies between this study and previous analyses. If the remainder of the controlled human exposure data become available, a new analysis may be useful.

Table 200. Tularemia Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 30 organisms Probit slope = 1.90 probits/log (dose)
• Post-exposure antibiotics	Rate (efficacy)	100%
Lethality	Rate	75%
Incubation period		
Dose < 106,604 organisms	Log-linear function	m = –0.8207 days/log (dose) b = 6.538 days (range: 3–7 days)
106,604 organisms ≤ dose < 9,019,577 organisms	Log-quadratic function	a = 0.1763 days/(log (dose))^2 b = –2.589 days/log (dose) c = 10.96 days (range 2–3 days)
Dose ≤ 9,019,577 organisms	Constant	1.5 days
Duration of illness		
• Stage 1 (non-survivors)	Constant	9 days
• Stage 2 (non-survivors)	Constant	6 days
• Stage 1 (survivors)	Constant	12 days
• Stage 2 (survivors)	Constant	28 days
• Stage 3 (survivors)	Constant	84 days
• Total duration after initiation of antibiotics (treated survivors)	Constant	10 days

Table 201. Tularemia Injury Profile

	Stage 1 (all)	Stage 2 (non-survivors)	Stage 2 (survivors)	Stage 3 (survivors)

Signs and symptoms (S/S)	High fever, headache, chills, sore throat, myalgia, chest pain	Stage 1 S/S plus severe pneumonia, respiratory distress	Stage 1 S/S plus mild pneumonia	Malaise, severe weakness
S/S Severity	3 (Severe)	4 (Very Severe)	3 (Severe)	2 (Moderate)

Cohorts and Special Considerations (*AMedP-7.5 Section 5.2.8.3*)

The definitions of the cohorts are sufficiently explained in *AMedP-7.5*. This section explains the equations used to calculate the cohort populations; for definitions of the variables in the equations, see *AMedP-7.5*.

For each equation, the essential question is how the value of $d_{trt\text{-}tul}$ compares to the time at which individuals in each dose range enter the next phase of disease (whether that be a stage, death, or RTD). The untreated fatality cohort $F_{DR,U}$ also depends upon the CFR. Several other equations subtract the population of $F_{DR,U}$ so that nobody is double counted.

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1.26. Smallpox Model
(*AMedP-7.5 Sections 5.2.9 and 5.2.10*)

Introduction

Smallpox is caused by the Orthopox virus, *variola*, of which there are at least two strains, *variola major* and *variola minor*. The World Health Organization (WHO) successfully eradiated the disease by 1980, through a program involving ring vaccination surrounding every known or suspected case of smallpox; the last recorded case of smallpox occurred in 1977. While poxviruses infect many zoonotic hosts, the *variola* virus only infects humans; there are no animal reservoirs to reintroduce the virus to the human population. Despite this, the potential use of *variola* as a biological weapon continues to pose a military threat. This threat can be attributed to the aerosol infectivity of the virus, the relative ease of large-scale production, the rate of human-to-human transmission, and an increasingly Orthopox virus-naive populace. Although the fully developed cutaneous eruption of smallpox is unique, earlier stages of the rash could be mistaken for other diseases.

Smallpox presents in a variety of clinical forms, the prevalence and prognosis of each depending on the vaccination status of the individual. Classic or ordinary type occurs in nearly 90% of unvaccinated cases and 70% of vaccinated cases. Flat-type and hemorrhagic types of smallpox occur less frequently and generally in individuals with an underlying immune deficiency; for example, hemorrhagic smallpox is seen disproportionately in pregnant women and flat-type in children. Both forms are associated with a severe toxemia that typically causes death 6 to 10 days after onset. Together these types account for 10% of unvaccinated cases and have nearly 100% case fatality rates; among vaccinated cases the combined frequency is approximately 5% but case fatality rates remain very high, from 67% to 94% depending on type. Modified type smallpox occurs in only 2% of unvaccinated cases but 25% of vaccinated cases; this type of smallpox resembles the classic or ordinary form but is milder in all respects and is nonfatal.[912]

Given its prevalence, the *AMedP-7.5* model focuses on ordinary type smallpox.

Assumptions (*AMedP-7.5 Section 5.2.9.2 and 5.2.10.2*)

Assumption: Inhalation of *V. major* results in "ordinary-type" (discrete) smallpox.

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912 This paragraph comprises several paraphases and summaries of information from A.R. Rao, *Smallpox* (Bombay: The Kothari Book Depot, 1972), 8–28. His observations are based on almost 7,000 personally observed cases.

As described in the introduction to this chapter, ordinary type smallpox is by far the most common presentation of disease, particularly for the military population.

> **Assumption**: Vaccination of all personnel is performed on the same day—$d_{vac\text{-}spox}$.

Although this may not be possible in reality, there is no practical way to implement phased vaccination in portions of the population within the methodology.

> **Assumption**: Personnel receiving post-exposure vaccination have no history of smallpox vaccination.

This is relevant because history of prior smallpox vaccination affects efficacy. We assume no prior vaccination because routine vaccination of civilians no longer occurs, and routine vaccination of military personnel should be modeled using pre-exposure vaccination.

> **Assumption**: Although smallpox survivors go through three stages of illness, the SEIRP model is a two-stage model. Thus, survivors who are CONV are modeled to move to the $R_S(d)$ cohort, under the assumption they are not contagious.

See Subsection 0.

Human Response Model (*AMedP-7.5 Tables 5-77 to 5-79, and 5-84 to 5-86*)

Infectivity

Because smallpox is exclusively a human disease, it has been impossible to develop an appropriate animal model for infectivity. Research suggests that each particle contains a single virion and that individual particles, deposited in the correct location, can cause infection.[913] This single deposited particle must likely be one of a number of inhaled particles that are retained in the lungs.

Note that in planning for Dark Winter, a Top Officials Exercise, the infectious dose of smallpox was assumed to be low based on the *JAMA Consensus Statement on Smallpox*,[914] which cited a 1970 study of a smallpox epidemic in a hospital in Meschede,

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913 Robert F. Parker, "Statistical Studies of the Nature of the Infectious Unit of Vaccine Virus," *Journal of Experimental Medicine* 67, no. 5 (1938): 726; and F. Fenner et al., *Smallpox and its Eradication* (Geneva, Switzerland: World Health Organization, 1988), 187–188.

914 Tara O'Toole, Michael Mair, and Thomas V. Inglesby, "Shining Light on 'Dark Winter'," *Clinical Infectious Diseases* 34, no. 7 (2002): 972–983.

Germany: "The infectious dose is unknown but is believed to be only a few virions."[915] The cited article, however, makes no specific reference to infectious dose; rather, the low required infectious dose is likely inferred from the disease spread and a smoke experiment showing the spread through the hospital.[916]

The only cited values for smallpox infectivity that we were able to locate were those published in reference to clinical recognition and management of multiple biological agents. The document cites an "assumed low (10–100 organisms)" infectious dose.[917] No specific reference is given for this value.

With no published data to support or challenge the value cited by Franz et al., infectivity is modeled as a threshold dose-response probability function: if the dose is greater than or equal to 10 PFU, an individual will be modeled as infected and later symptomatic with probability = 1; if the dose is less than 10 PFU, the probability of infection and later symptoms is 0. The threshold infectious dose of smallpox is a conservative selection based on the assumed infectious dose range of 10–100 organisms. It is also consistent with the idea that 1 virion can cause infection, if one assumes that 10% of what is inhaled will be retained.

Lethality

Rao provides CFR statistics for thousands of cases, and Fenner et al.[918] quote Rao when giving information on the CFR. In 3,147 unvaccinated ordinary type smallpox cases personally observed by Rao, the CFR was 30.2%.[919] The 30.2% CFR includes people of all age groups, so we also consulted a later table in Rao's document that shows the number of cases and deaths for different age groups.[920] Although Rao included data for younger and older populations, only the pertinent data are reproduced in Table 202 (since 45+ are all grouped by Rao, and this could potentially include many people beyond military age, the 45+ group is not included here). Although there is some variation within the age groups, the net CFR among the whole population (n = 825) considered in Table 202 rounds to 30%, just like the overall CFR reported by Rao for 3,147 individuals.

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915 Donald A. Henderson et al., "Smallpox as a Biological Weapon: Medical and Public Health Management," *Journal of the American Medical Association* 281, no. 22 (June 1999): 2129.

916 P. F. Wehrle et al., "An Airborne Outbreak of Smallpox in a German Hospital and its Significance with Respect to Other Recent Outbreaks in Europe," *Bulletin of the World Health Organization* 43, no. 5 (1970): 669–679.

917 Franz et al., "Clinical Recognition and Management," 400–401.

918 Fenner et al., *Smallpox and its Eradication*, Table 1.2.

919 Rao, *Smallpox*, 8.

920 Rao, *Smallpox*, Table 17.1. Rao also provides data on the CFR for other types of smallpox and in various subpopulations, but that information is not relevant here.

Since there is no larger dataset than that provided by Rao, *AMedP-7.5* uses his data, which gives a rounded CFR of 30%. This is the same value reported in *MMBC*.[921] The CFR for vaccinated individuals is discussed in Subsection 0.

Table 202. CFR Data from Rao for Ordinary Type Smallpox in Unvaccinated Individuals of Military Age

	Age Range					
	20–24	**25–29**	**30–34**	**35–39**	**40–44**	**All**
Cases	132	83	50	30	30	825
Deaths	39	24	12	14	10	99
CFR (%)	29.5	28.9	24.0	46.7	33.3	30.4

Incubation Period

Because smallpox is a contagious disease, and one not well-modeled by an existing animal model, it is difficult to determine an exact incubation period. Data collected from multiple outbreaks suggest that the typical incubation period for smallpox is 10–14 days but may be as short as 7 days or as long as 19 days.[922]

We combined two datasets that provide incubation period data for unvaccinated cases. One set of data was prepared for the World Health Organization[923] and consisted of a study of 175 cases spread across Kosovo, Serbia, Voivodina, and Montenegro; the incubation period for 171 of these cases was captured. The second dataset comes from a compilation of 898 cases including *variola major* and *variola minor* collected by multiple authors;[924] we used the incubation period for 61 unvaccinated cases of *variola major*. Table 203 summarizes the full dataset we used to derive the incubation period model. Fitting the Table 203 data to a lognormal distribution gives the following model: mean 11.6 days, standard deviation 1.8 days, $\mu = 2.439$, $\sigma = 0.154$.

Recall that the SEIRP model has a parameter for the minimum incubation period and a second parameter to model the remainder of the time. Since the minimum incubation period observed in the underlying data was 7 days, the value of μ_{E1} for smallpox is 7 days. Thus, the value of μ_{E2} is 4.6 days. Note that the SEIRP model's construction is such that the time spent in the E_2 cohort is modeled as an *exponential* distribution with a mean of 4.6 days, instead of a lognormal distribution.

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921 USAMRIID, *Medical Management of Biological Casualties*, 88.

922 Fenner et al., *Smallpox and its Eradication*, 188.

923 S. Litvinjenko, B. Arsic, and S. Borjanovic, "Epidemiologic Aspects of Smallpox in Yugoslavia in 1972," *Bulletin of the World Health Organization*, WHO/SE/73.57 (1973).

924 A. W. Downie, "Incubation Period in Smallpox," *Bulletin of the World Health Organization*, WHO/SE/72.3 (1972).

Table 203. Smallpox Incubation Period Data

Length of Incubation Period (days)	Number of Cases	
	Litvinjenko	Downie
7	1	0
8	5	3
9	20	3
10	26	3
11	39	5
12	39	12
13	27	18
14	6	9
15	7	7
16	1	0
17	0	1
Total Patients	171	61

Injury Profile

Smallpox is described as a tri-phasic disease for survivors and a bi-phasic disease for non-survivors. Following the incubation period, both profiles begin with a prodromal, febrile period (modeled as Stage 1), then progress to the rash stage with the outbreak of the maculopapular rash (modeled as Stage 2). Survivors progress to the recovery stage with scab formation and eventual scab separation (modeled as Stage 3).[925]

Dixon described two stages: pre-eruptive and eruption. The pre-eruptive stage is marked by the sudden onset of fever and malaise; symptoms similar to influenza may manifest in as little as an hour. Although unlikely, a small fraction of the population may exhibit a rash during this period. The rash begins in the mouth and throat, and then spreads to the body. It may spread uniformly or it may move downward from the face. The end result is a rash that "is more uniform in color than the rash of measles, has a centrifugal distribution, and quickly becomes papular."[926]

During the first stage, the disease may be difficult to diagnose based on clinical symptoms, which include fever and malaise, possibly accompanied by vomiting, muscle

925 Franz et al., "Clinical Recognition and Management," 404–405.

926 C. W. Dixon et al., "Smallpox in Tripolitania, 1946: An Epidemiological and Clinical Study of 500 Cases, Including Trials of Penicillin Treatment," *The Journal of Hygiene* 46, no. 4 (December 1948): 360–361.

ache, or headache. The suddenness of onset is one mark of the disease, with patients progressing from feeling well to feeling flu-like within an hour.[927]

The second stage of illness is marked by the formation or eruption of a macular rash; the exact onset of the second stage may be difficult to determine clinically because it requires identification of the earliest lesions, which may form in the larynx or mouth and may not be easily visible. While most experts agree that the rash begins in the mouth and throat, there is disagreement about how the rash spreads. Some explain that it moves downward from the face to the trunk and hands and then the feet. Others state that the rash forms first at the extremities and moves inward toward the trunk. The rash is distinguished from measles and other pox virus rashes by the centrifugal pattern and near uniformity of the macules. As the disease progresses, the rash becomes papular and then pustular.[928] Death, if it occurs, usually occurs in the second week of illness as a result of "toxemia associated with circulating immune complexes and soluble variola antigens."[929] "In the second week after onset, the pustules form scabs that leave depressed depigmented scars on healing,"[930] denoting survivors' progression into the third stage of illness.

Summarizing: the first stage of illness may include several flu-like symptoms, including fever, malaise, loss of appetite, and fatigue. The second stage is defined by the progression of the rash from macular to papular. The third stage, in survivors, involves the formation and eventual separation of scabs.

We assigned Injury Severity Level of 2 to Stage 1, consistent with fever and general flu-like symptoms, possibly with muscle or backache, headache, and vomiting. Likewise, for survivors we assigned Injury Severity Levels 3 to Stage 2, and CONV to Stage 3. For non-survivor, we assigned Injury Severity Level 4 to Stage 2. Table 204 and Table 205 are the smallpox Injury Profiles.

927 Franz et al., "Clinical Recognition and Management," 404.
928 Ibid.
929 Henderson et al., "Smallpox as a Biological Weapon," 2130.
930 Franz et al., "Clinical Recognition and Management," 404.

Table 204. Smallpox Non-Survivor Injury Profile

	Stage 1	Stage 2
Signs and Symptoms (S/S)	High fever (38–40.5 °C); malaise; vomiting; chills; headache; severe backache; possibly accompanied by abdominal pain and/or delirium	Fever falls but rises again and remains elevated; difficulty swallowing; enanthem over pharynx; appearance of maculopapular rash first on the face, hands, and forearms (including mouth and pharynx) and subsequently on lower extremities; within days, vesicles form and progress to pustules and then scars; severe systemic toxemia leads to multiple organ failure
S/S Severity	2 (Moderate)	4 (Very Severe)

Table 205. Smallpox Survivor Injury Profile

	Stage 1	Stage 2	Stage 3
Signs and Symptoms (S/S)	High fever (38–40.5 °C); malaise; vomiting; chills; headache; severe backache; possibly accompanied by abdominal pain and/or delirium	Fever decreases from peak levels (approx. 40 °C) and fluctuates throughout this stage; sore throat; enanthem over pharynx; appearance of maculopapular rash first on the face, hands, and forearms (including mouth and pharynx) and subsequently on lower extremities; within days, vesicles form and progress to pustules	General condition improves; scabs form in place of pustules and then separate leaving depressed, depigmented scars upon healing
S/S Severity	2 (Moderate)	3 (Severe)	CONV

Duration of Illness

Two compounding factors complicate derivation of the duration of illness model. First, an accurate detection of progression from one stage to the next relies heavily on patient initiative and promptness in reporting changes and, for the transition from Stage 1 to Stage 2, on the attentiveness of the physician in detecting the first lesion.[931] A patient or doctor expecting vesicles as the indication of smallpox may not identify them until midway through Stage 2, forcing epidemiologists to estimate the length of Stage 1. Second, since smallpox not only varies in type, but also in its symptomatic effect on each patient, research—particularly the studies conducted before 1950—may be vast in cases but irrelevant to examining the ordinary type.[932] Generally, research conducted was relevant, but excluded the underlying data themselves, such that we were forced to use estimates produced by others instead of performing a meta-analysis to determine our own values.

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931 Martin I. Meltzer, Inger Damon, James W. LeDuc, and J. Donald Millar, "Modeling Potential Responses to Smallpox as a Bioterrorist Weapon," *Emerging Infectious Diseases* 7, No. 6 (2001): 960.

932 Rao, *Smallpox*, 29.

Historical cases suggest that the prodromal period duration is approximately the same independent of whether an individual becomes a fatality or survives the disease and independent of smallpox type.[933] Reviewing data from several data sources and using temperature, versus enanthem, as the stage differentiator, Fenner et al. reported that the prodromal stage lasts 3 days.[934] Likewise, Bombardt calculated a 3-day mean prodromal period with a standard deviation of 0.95 days.[935] Other mean prodromal duration values ranged from 2.49 days (with a standard deviation of 0.88 days)[936] to 3 days.[937] Since 3 days seems to be the most commonly reported value, and the only source that reported 3 days and also reported a standard deviation is Bombart, we used his values for Stage 1: a 3-day mean and a standard deviation of 0.95 days. Applied to a lognormal distribution, this yields the parameters $\mu = 1.051$, $\sigma = 0.309$.

Eichner and Dietz estimated the mean duration of Stage 2 as 16 days,[938] while Rao suggests a shorter duration of 12 to 14 days post-symptom onset, or 10 to 12 days post-Stage 1 (based on a postulate 2-day prodrome).[939] Meltzer et al., found the duration of the second stage to be from 10 to 15 days.[940] The range of mean values reported is 10–16 days; we chose 14 days for the *AMedP-7.5* model because it is near the middle of the reported range, and it corresponds to one of the values used by Bombardt (other values were 7 and 12 days),[941] such that (1) there is consistency between the Stage 1 and Stage 2 models, and (2) it is possible to estimate an associated standard deviation (which is neither provided by nor estimatable from the reports of most of the other authors).

Bombardt discussed two outbreaks in his paper: one in Sweden in 1963 and the other in Yugoslavia in 1972. We used Bombardt's model from the Yugoslavian outbreak because it was the largest outbreak for which the necessary data are available, with 175 cases in

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933 Henderson et al., "Smallpox as a Biological Weapon," 2129–2130; Fenner et al., *Smallpox and its Eradication*; Rao, *Smallpox,* 11–12; Peter B. Jahrling et al., "Smallpox and Related Orthopoxviruses," chap. 11 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), 215–240.

934 Fenner et al., *Smallpox and its Eradication*, Fig 1.1.

935 Bombardt, *Smallpox Transmission*, Figure II-7.

936 Martin Eichner and Klaus Dietz, "Transmission Potential of Smallpox: Estimates Based on Detailed Data from an Outbreak," *American Journal of Epidemiology* 158, no. 2 (2003): Table 3.

937 Based on case studies collected by Justus Strom and Bo Zetterberg, *Smallpox Outbreak and Vaccination Problems in Stockholm, 1963* (Stockholm, Kungl. Boktryckeriet P.A. Norstedt & Soner, 1966), 45–56.

938 Eichner and Dietz, "Transmission Potential of Smallpox," Table 3.

939 Rao, *Smallpox,* 22.

940 Meltzer et al., "Modeling Potential Responses to Smallpox," 960.

941 Bombardt, *Smallpox Transmission*, 29.

total. Bombardt modeled the Yugoslavian outbreak using two distributions: combined incubation and prodrome (or Stage 1) and infection-to-removal time (from infection until the end of Stage 2, since "removal" means no longer transmitting disease). He used a 15-day mean and 2-day standard deviation for combined incubation and prodrome.[942] The 15-day mean corresponds well to the *AMedP-7.5* mean of 11.6 days for incubation plus the 3-day mean for Stage 1. Bombardt modeled the mean infection-to-removal time with three different values: 22, 26, and 29 days, corresponding to a Stage 2 durations of 7, 11, and 14 days. We have already chosen a Stage 2 duration of 14 days. The corresponding standard deviation for infection-to-removal time in Bombardt's model is 3 days. We calculated the standard deviation for Stage 2 alone according to Equation 20, deriving a value of 2.24 days (standard deviation to mean ratio of 0.16), which is not far off from Eichner and Dietz's estimate of 2.83 days with a mean of 16 days (standard deviation to mean ratio of 0.177).[943] Thus, the final Stage 2 duration of illness model is a lognormal distribution with a mean of 14 days and a standard deviation of 2.24 days (μ = 2.626, σ = 0.159)

$$\sigma_{Stg2} = \sqrt{(\sigma_{\text{infection-to-removal}})^2 - (\sigma_{\text{incubation+prodrome}})^2} = \sqrt{(3\text{ days})^2 - (2\text{ days})^2} = 2.24\text{ days} \quad (20)$$

The third stage is not as well described in research, presumably because it only involves survivors who are no longer contagious, and therefore of less interest to epidemiologists. However, Fenner et al. concluded on the basis of clinical experience that the duration of the "scabbing" phase is 5 days.[944] In contrast, the *JAMA Consensus Statement on Smallpox* indicates that the duration of Stage 3 is 7 days,[945] but it also reports a shorter duration for Stage 1, so the longer Stage 3 may be simply to account for the well-recognized total duration of illness from other sources like Fenner. *AMedP-7.5* uses the Fenner et al. estimate of 5 days, with a fixed-duration model instead of a probability distribution.

Contagious Spread Parameters for the SEIRP Model

The two parameters for which values must be derived are α (single value) and β (function of time post-incident).

The Relative Infectiousness (α)

Most sources agree that the disease is most infectious during the period immediately after the rash forms in the mouth and pharynx; these eruptions lead to respiratory virus

942 Ibid., Table III-1.

943 Eichner and Dietz, "Transmission Potential of Smallpox," Table 3.

944 Fenner et al., *Smallpox and its Eradication*, Fig 1.1.

945 Henderson et al., "Smallpox as a Biological Weapon," Figure 1.

secretions that are exhaled.[946] Although other means of transmission exist, the respiratory secretions are believed to be the most common form of disease spread.[947] Note that researchers often refer to the period of highest infectivity as occurring during "the first week of illness." This often coincides with the assumption that illness actually begins with rash formation and disregards the febrile symptoms observed during the prodromal period. Mack, Thomas, and Khan summarized this by stating, "in none [of the curves depicting disease transmission] is there a suggestion of significant transmission during the prodromal period."[948]

These results indicate that during the prodromal or first stage of illness, an infected individual is unlikely to be infectious. Although the CDC extends the duration of the contagious period to throughout recovery—"The person is contagious to others until all of the scabs have fallen off"[949]—scholars consider scab shedding "not highly infectious."[950] Thus, although there is a Stage 3 for smallpox survivors, the definition of α need only relate to Stages 1 and 2, and the value for smallpox should be 0 because individuals in Stage 1 (I_1 cohort) are not expected to spread disease to individuals in the susceptible cohort. All contagious spread in the model will occur as a result of the I_2 cohort.

The Time-Varying Rate of Disease Transmission (β)

In Subsection 0 we discussed the time dependence of the disease transmission rate during an epidemic and we mentioned that it is not known beforehand. On the other hand, the epidemic curve for a carefully selected historical outbreak and additional epidemiological data can be coupled with an epidemic model to determine a driving time-dependent rate of disease transmission. And with regard to either primary pneumonic

946 Fenner et al., *Smallpox and its Eradication,* 189; Henderson et al., "Smallpox as a Biological Weapon," 2130. Note that Dixon believes that contact during the pre-eruptive (or prodromal) stage is the most likely to cause transmission. He argues, however, that respiratory spread due to virus in the respiratory system is the likely source of infection spread; this actually seems to correspond to the early eruptive stage, after the rash has developed in the mouth and throat but before the rash has spread to the dermis. Dixon et al., "Smallpox in Tripolitania," 370–71.

947 Franz et al., "Clinical Recognition and Management," 404.

948 Thomas M. Mack, David B. Thomas, and M. Muzaffar Khan, "Epidemiology of Smallpox in West Pakistan: II. Determinants of Intravillage Spread Other than Acquired Immunity," *American Journal of Epidemiology* 23, no. 2 (1972): 169–77.

949 Centers for Disease Control and Prevention (CDC), "Small Pox Disease Overview," last updated January 15, 2016, http://emergency.cdc.gov/agent/smallpox/overview/disease-facts.asp.

950 Fenner et al., *Smallpox and its Eradication*, 189. Similar statements are made by other scholars: Henderson et al., "Smallpox as a Biological Weapon," 2129; Meltzer et al., "Modeling Potential Responses to Smallpox," 960; Eichner and Dietz, "Transmission Potential of Smallpox," 115.

plague or smallpox, it is assumed that such a historical transmission rate is at least indicative of potential outbreak dynamics in a military population.

Of particular interest here is the 1972 smallpox outbreak in Yugoslavia.[951] From 1932 to 1972, Yugoslavian health care systems did not have to deal with smallpox cases, and this smallpox-free period of 40 years undoubtedly fostered a false sense of security. Even though vaccinations of Yugoslavian children continued unabated, the declining vaccinal state of Yugoslavia's adult population was an important factor behind the 1972 outbreak, which began with a single index case and involved a total of 175 smallpox cases.

The derivation of β for a historical smallpox outbreak is essentially the same as that for a historical outbreak of primary pneumonic plague. One important common feature is the characterization of the incubation period distribution in Monte Carlo calculations. Random draws from a lognormal (or other familiar continuous) distribution may well yield unrealistic incubation periods: either shorter than the shortest observed period or longer than the longest observed period. To preclude unrealistic incubation periods in Monte Carlo calculations, we used a triangular incubation period distribution with nonzero, finite endpoints at the shortest and longest observed periods for the purpose of deriving values of β for the Yugoslavian outbreak (values in *AMedP-7.5* Table 5-85). The next paragraph shows that only a small error is introduced by using the triangular distribution.

Figure 14 shows three different cumulative distributions of smallpox incubation periods. Points in this figure are based on the data in Table 203; the magenta curve corresponds to the lognormal probability density function (PDF) that is defined on the basis of the Table 203 data (see Subsection 0), and the blue curve comes from a triangular PDF where 7 days ≤ incubation period ≤ 17 days (corresponding to Table 203). The data and the two distributions all have a mean value of 11.6 days. *AMedP-7.*5 Table 5-85 lists derived time-dependent values of β for the 1972 smallpox epidemic in Yugoslavia.

951 Bombardt, *Smallpox Transmission*. The rest of this paragraph is paraphrased from this source.

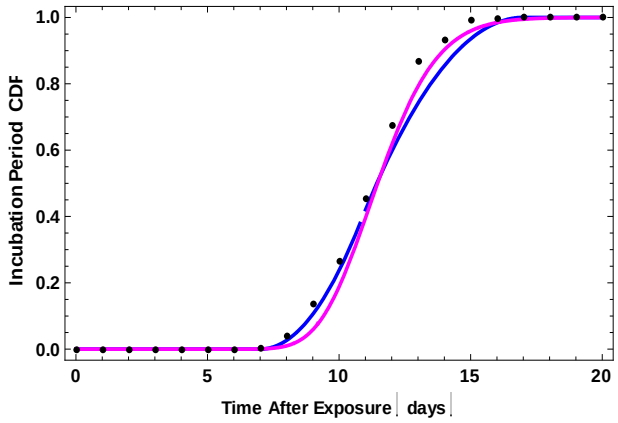

Figure 14. Three Cumulative Distributions of the Smallpox Incubation Period Resulting from Data (points), Lognormal PDF (magenta curve), and Triangular PDF (blue curve)

Medical Countermeasures and Treatment Model

Because smallpox is highly contagious, the objective of medical management is to limit the spread of the disease by isolating patients and vaccinating at-risk individuals. No antiviral drug treatment is available for smallpox.

Pre-Exposure and Post-Exposure Vaccination

Although the specific formulation has changed over time, historical vaccines (such as Dryvax) and the modern vaccine (ACAM200) contain live *vaccinia* virus, a poxvirus that induces protection against smallpox. Pre-exposure vaccination, often—but not always—combined with isolation and quarantine, played a crucial role in the control of historical outbreaks and eventual eradication of smallpox.[952]

A review of smallpox cases and their spread—with and without vaccination—evaluated the rate of protection afforded by vaccination for eight outbreaks researched by numerous authors, as summarized in Table 206.[953] The rate of protection was calculated as one minus the ratio of percentage of vaccinated contacts with smallpox to percentage of unvaccinated contacts with smallpox.[954] The resulting rates of protection varied from 40% to more than 95%. The study's authors then reevaluated using only the outbreaks involving substantial numbers of smallpox contacts (100 or more contacts, calculated by summing the two "total # contacts" rows for each outbreak). This reevaluation resulted in rates of protection between 90.7% and 97.2%.[955]

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952 Fenner et al., *Smallpox and its Eradication*, 590.

953 Ibid., 200 and 591.

954 Rate of protection by vaccination = 100% × [1 – (% of vaccinated contacts with smallpox/% of unvaccinated contacts with smallpox)].

955 Fenner et al., *Smallpox and its Eradication*, 590–591; Bombardt, *Smallpox Transmission*, 39–43.

Table 206. Efficacy of Smallpox Pre-Exposure Vaccination

Outbreak Location	Vaccination Scar?[a]	Total # Contacts	Smallpox Cases Among Contacts		Rate of Protection (%)
			Number	%	
Benin	-	17	8	47.1	67.3
	+	13	2	15.4	
Bangladesh	-	21	9	42.9	83.6
	+	57	4	7.0	
Calcutta	-	80	61	76.3	90.7
	+	661	47	7.1	
Madras	-	103	38	36.9	96.7
	+	1146	14	1.2	
Nigeria	-	27	12	44.4	40.0
	+	45	12	26.7	
Punjab Province, Pakistan	-	45	33	73.3	95.7
	+	190	6	3.2	
Punjab Province, Pakistan	-	22	10	45.5	97.1
	+	238	3	1.3	
Shelkhupura District, Pakistan	-	43	38	88.4	91.9
	+	180	13	7.2	

[a] Used by Fenner et al. as a surrogate for successful vaccination, although they noted it is possible that the scar could form for other reasons (p. 590), leaving someone counted as immunized in this table actually susceptible. Thus, the analysis related to these numbers could underestimate vaccine efficacy.

Grouping the data for outbreaks with greater than 100 contacts, there were 293 unvaccinated (no scar) contacts, 180 of which developed smallpox (61.4%), and 2,415 vaccinated (scar) contacts, 83 of which developed smallpox (3.4%). From these data, the pre-exposure vaccination efficacy according to the equation stated previously is 94.4%. To avoid false precision and for simplicity, this is rounded to 95% for *AMedP-7.5*. This value is also consistent with the "take rate" observed in a subset of U.S. military vaccinees in the early 2000's (95.5% take rate in 1017 primary vaccinees and 95.8% take rate in 975 people vaccinated decades earlier).[956]

AMedP-8(*C*) modeled a fixed 85% efficacy for post-exposure prophylaxis, independent of time since exposure, but clearly stated the basis for this was merely

956 John D. Grabenstein and Willian Winkenwerder, "US Military Smallpox Vaccination Program Experience," *Journal of the American Medical Association* 289, No. 24 (2003): 3279

assumption. However, the efficacy of post-exposure prophylaxis depends on the time elapsed since exposure. The *JAMA Consensus Statement on Smallpox* states that "vaccination administered within the first few days after exposure and perhaps as late as 4 days may prevent or significantly ameliorate subsequent illness,"[957] citing Dixon. Dixon states that longer duration between exposure and vaccination correlates with lower efficacy.[958] Fenner states, "following primary vaccination, no antibody was detected up to the 10th day, after which neutralizing and HI antibodies were present in the majority of individuals and CF antibodies in less than half,"[959] so the likely reason for decreased efficacy over time is that the longer the delay in vaccination, the more probable the incubation period will end before sufficient immune response has been mustered.[960]

We considered modeling the onset of immune response over time as a means of generating a table of post-exposure prophylaxis efficacy over time, but found that the overall immune response to smallpox vaccination is too complex, given the data available. Although we could model immunoglobulin M (IgM) production over time, IgM alone does not give immunity; rather, cell-mediated immunity also plays an important role, but not much is known about exactly how the various components of immunity combine to produce an effective immune response.

Further, although many animal models have been used in attempts to model different aspects of smallpox infection in humans, because different orthopoxviruses must be used for animal models, the applicability of such data is limited.

Since there are no proper data that could be used, we turned to SME estimates. Massoudi, Barker, and Schwartz conducted a Delphi analysis[961] based on the input of nine public health officials who participated in smallpox eradication activities, specifically for the purpose of providing parameter values needed for mathematical modeling. Although there were only nine respondents for the analysis and uncertainty must therefore be considered high, there is no other feasible way to generate an estimate for *AMedP-7.5*.

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957 Henderson et al., "Smallpox as a Biological Weapon," 2132.

958 Dixon et al., "Smallpox in Tripolitania," 370.

959 Fenner et al., *Smallpox and its Eradication*, 158.

960 The statement that post-exposure vaccination is protective "perhaps as late as 4 days" post-exposure is likely related to the approximately 10-day timeline to protective immunity and the incubation period being reported as 12 to 14 days in the *JAMA Consensus Statement* (4 days post exposure + 10 days to generate immunity = 14 days).

961 Delphi analysis is "a method to systematically obtain expert opinion and build consensus in a way that maximizes the impact of the strength of experts' arguments while minimizing that of individual personalities and group dynamics", according to Mehran S. Massoudi, Lawrence Barker, and Benjamin Schwartz, "Effectiveness of Postexposure Vaccination for the Preventation of Smallpox: Results of a Delphi Analysis," *The Journal of Infectious Diseases* 188, No. 7 (2003): 973.

The authors of the Delphi study tabulated the SME estimates and calculated the 25th, 50th, and 75th percentiles for each time point. Table 207 summarizes the results for disease-prevention efficacy for people with no prior vaccination history. Since *AMedP-7.5* uses a 1-day time resolution, we combined the first two rows into a "Day 1" category and assigned an efficacy of 90%. Since "Day 2" in *AMedP-7.5* means that 1 day has passed since the challenge event (and so forth for other days), the time points as given by Massoudi, Barker, and Schwartz must be adjusted to be on the same "scale" as *AMedP-7.5*; this is reflected by the second column in Table 207. The 50th percentile efficacies for the third through fifth rows were used as is for *AMedP-7.5* Table 5-78.

Table 207. Results of Delphi Analysis for Post-Exposure Vaccination Efficacy Over Time

Time Between Exposure and Vaccination	*AMedP-7.5* Day	SME Estimate of Efficacy		
		25th Percentile	50th Percentile	75th Percentile
0–6 hours	1	75	93	98
6–24 hours		65	90	95
1–3 days	2–4	55	80	89
4–7 days	5–8	8	25	35
8–14 days	9–15	0	2	8

Although the different efficacies are straightforward to implement when using the isolation/quarantine smallpox model, it is more complicated for the SEIRP model. Since the SEIRP model cannot track individuals and there may be multiple generations of infection all at different stages of progression through disease, there is no way to estimate the subpopulation to which a given time-dependent efficacy should apply without adding additional equations to the SEIRP model. Although we do recommend that for the next version of *AMedP-7.5*, a better epidemic model be created such that time-varying efficacy (and other enhancements) can be included, it is not feasible for this version. Thus, as a rough approximation, recognizing that there is inherent error in this approach, the model simply applies the values from Table 207 without attempting to account for the multiple generations of disease. When vaccination is delayed by several weeks, this could significantly underestimate the efficacy of vaccination. Thus, this model is best used early in the epidemic. Note that on the day post-exposure prophylaxis is applied to the E cohort, pre-exposure prophylaxis will also be applied to the S cohort (as indicated by the presence of the term $\left(1 - \rho_S \cdot \nu_{on}(d\text{-}1)\right)$ in *AMedP-7.5* Equation 5-13.

Lethality

In addition to reporting CFR data for the unvaccinated (see Subsection 0), Rao also reported CFR information for vaccinated individuals. Although he also presented information for other presentations of smallpox, Table 208 presents Rao's data for only the ordinary-type cases.[962] Note that unvaccinated individuals are included for reference, and that the CFR among unvaccinated individuals in this dataset is slightly higher than the CFR discussed in Subsection 0. Since the value discussed in Subsection 0 is based on a larger dataset and there is an unknown degree of overlap the two datasets, the unvaccinated CFR is included in Table 208 only as confirmation that the outbreak represented by the Table 208 data was not abnormal.

Table 208. Ordinary Type Smallpox Case Fatality Rate Data for Vaccinated Individuals

Vaccinal Status	# Cases	CFR (%)
Unvaccinated	1296	36.9
Unsuccessfully vaccinated	1425	27.2
Primary vaccination after exposure	426	20.6
Primary vaccination before exposure	2302	3.3

Based on Table 208, *AMedP-7.5* uses two different vaccination-related CFRs. Individuals who receive effective pre-exposure vaccination have a CFR of 3%. Those who receive post-exposure vaccination or ineffective pre-exposure vaccination have a CFR of 20%. Ideally, the CFR for post-exposure vaccinated individuals should be dependent on the time elapsed since exposure, but no data were available to create such a model.

Although the different CFRs are straightforward to implement when using the isolation/quarantine smallpox model, it is more complicated for the SEIRP model. Since the SEIRP model cannot track individuals and there may be multiple generations of infection, some simplification must be done to use a time-varying CFR. The concept is to take a weighted average of the three CFRs, with the "weight" for each CFR being the probability that the given CFR should apply. Recall that the user must specify the day on which vaccination occurs ($d_{vac\text{-}spox}$) and that vaccination is assumed to occur in the entire population on the same day.

- The probability that the unvaccinated CFR should apply equals the probability that the individual was in an I cohort on $d_{vac\text{-}spox}$.

962 Rao, *Smallpox*, Table 5.1.

  - This is equivalent to the probability that the duration of Stage 1 + Stage 2 was ≥ the time elapsed since $d_{vac\text{-}spox}$.
    - This can be calculated by convolving the Stage 1 and Stage 2 durations of illness and calculating 1 minus the CDF, as a function of days since $d_{vac\text{-}spox}$.
- The probability that the post-exposure vaccination CFR should apply equals the probability that the individual was in an E cohort on $d_{vac\text{-}spox}$.
  - This is equivalent to the probability that the duration of Stage 1 + Stage 2 was < the time elapsed since $d_{vac\text{-}spox}$ and that the duration of the incubation period + Stage 1 + Stage 2 was ≥ the time elapsed since $d_{vac\text{-}spox}$.
    - This can be calculated by convolving the Stage 1 and Stage 2 durations of illness and multiplying that CDF by 1 minus the CDF of the incubation period, Stage 1, and Stage 2 all convolved together.
- The probability that the pre-exposure vaccination CFR should apply equals the probability that the individual had not yet been exposed on $d_{vac\text{-}spox}$, which can be calculated by subtracting the other two calculated probabilities from 1.

To represent how the distributions are included in the SEIRP model, the above calculations were completed using exponential distributions to model the incubation period, Stage 1, and Stage 2 of illness, with the exponentially distributed incubation period having a mean of 4.6 days, and then adding a constant value of 7 days to the result. Table 209 shows the results of the process described above. The first and last columns are used to construct *AMedP-7.5* Table 5-86.

Table 209. Calculation of Smallpox CFR to be Applied in SEIRP Model by Day

Days since $d_{vac\text{-}spox}$	Probability: in I Cohort on $d_{vac\text{-}spox}$	Probability: in E Cohort on $d_{vac\text{-}spox}$	Probability: in S Cohort on $d_{vac\text{-}spox}$	Day's CFR (calculated)
1–2	0.99–0.96	0.01–0.04	0.00	0.30
3–4	0.93–0.88	0.07–0.12	0.00	0.29
5–6	0.84–0.79	0.16–0.21	0.00	0.28
7–8	0.75–0.70	0.25–0.30	0.00	0.27
9–10	0.66–0.61	0.34–0.37	0.01	0.26
11–12	0.57–0.54	0.40–0.43	0.02–0.04	0.25
13	0.50	0.45	0.05	0.24
14–15	0.47–0.43	0.46–0.47	0.08–0.10	0.23
16	0.40	0.47	0.13	0.22

Days since $d_{vac\text{-}spox}$	Probability: in I Cohort on $d_{vac\text{-}spox}$	Probability: in E Cohort on $d_{vac\text{-}spox}$	Probability: in S Cohort on $d_{vac\text{-}spox}$	Day's CFR (calculated)
17	0.38	0.47	0.16	0.21
18–19	0.35–0.33	0.46–0.45	0.19–0.22	0.20
20	0.30	0.44	0.25	0.19
21	0.28	0.43	0.29	0.18
22	0.26	0.41	0.32	0.17
23–24	0.25–0.23	0.40–0.38	0.35–0.39	0.16
25	0.21	0.37	0.42	0.15
26–27	0.20–0.19	0.35–0.33	0.45–0.48	0.14
28	0.17	0.32	0.51	0.13
29–30	0.16–0.15	0.30–0.28	0.54–0.57	0.12
31–32	0.14–0.13	0.27–0.25	0.59–0.62	0.11
33–34	0.12–0.11	0.24–0.23	0.64–0.66	0.10
35–37	0.10–0.09	0.21–0.19	0.68–0.72	0.09
38–40	0.08–0.07	0.18–0.15	0.74–0.77	0.08
41–43	0.07–0.06	0.14–0.13	0.79–0.81	0.07
44–48	0.05–0.04	0.12–0.09	0.83–0.87	0.06
49–56	0.04–0.02	0.08–0.05	0.88–0.92	0.05
57–71	0.02–0.01	0.05–0.02	0.93–0.97	0.04
≥72	0.01–0.00	0.02–0.00	0.98–1.00	0.03

Note: The CFR associated with being in the I cohort on $d_{vac\text{-}spox}$ is 30%, the CFR associated with being in the E cohort on $d_{vac\text{-}spox}$ is 20%, and the CFR associated with being in the S cohort on $d_{vac\text{-}spox}$ is 3%.

Parameters for the SEIRP Model

Several SEIRP model parameters relate to the medical treatment model. First, parameter μ_{RS}, which is the fixed time individuals spend in the removed survivor, no longer contagious cohort ($R_S(d)$), is 5 days, consistent with the duration of illness model (Stage 3) and with the fourth assumption stated under Section 0. Second, the parameter MT_{I1}, which indicates whether medical treatment causes ill personnel in Stage 1 to no longer transmit disease despite remaining symptomatic (and therefore move into $R_S(d)$), is 0, because there is no treatment that has the stated effect for individuals ill with smallpox (the parameter is included in the model because it is relevant for plague).

Model Summary

Table 210 through Table 212 summarize the model parameters for modeling smallpox with effective isolation/quarantine in *AMedP-7.5*, and Table 213 summarizes the model parameters for modeling smallpox using the SEIRP model in *AMedP-7.5*. Recognizing the unlikeliness of new data ever becoming available, we nevertheless note that this model

would be improved by data-supported estimates of the infectivity, duration of Stage 3 of illness, and post-exposure vaccination efficacy as a function of time. Further, a contagious disease model that does not rely on historical outbreaks for modeling the rate of disease spread would be an improvement over the current SEIRP model.

Table 210. Smallpox Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Threshold	10 PFU
• Pre-exposure vaccination	Rate (efficacy)	95%
• Post-exposure vaccination	Time-varying rate (efficacy)	See Table 207
Lethality[a]		
• Unvaccinated	Rate	100%
• Vaccinated before exposure	Rate	3%
• Vaccinated after exposure	Rate	20%
Incubation period	Lognormal distribution	Mean = 11.6 days Standard deviation = 1.8 days μ = 2.439; σ = 0.154
Duration of illness		
• Stage 1	Lognormal distribution	Mean = 3.0 days Standard deviation = 0.95 days μ = 1.051; σ = 0.309
• Stage 2	Lognormal distribution	Mean = 14.0 days Standard deviation = 2.24 days μ = 2.626; σ = 0.159
• Stage 3 (survivors)	Constant	5 days

[a] Note that implementation for the SEIRP model is via *AMedP-7.5* Table 5-86, as explained in Subsection 0 of this TRM.

Table 211. Smallpox Non-Survivor Injury Profile

	Stage 1	Stage 2
Signs and Symptoms (S/S)	High fever (38–40.5 °C); malaise; vomiting; chills; headache; severe backache; possibly accompanied by abdominal pain and/or delirium	Fever falls but rises again and remains elevated; difficulty swallowing; enanthem over pharynx; appearance of maculopapular rash first on the face, hands, and forearms (including mouth and pharynx) and subsequently on lower extremities; within days, vesicles form and progress to pustules and then scars; severe systemic toxemia leads to multiple organ failure
S/S Severity	2 (Moderate)	4 (Very Severe)

Table 212. Smallpox Survivor Injury Profile

	Stage 1	Stage 2	Stage 3
Signs and Symptoms (S/S)	High fever (38–40.5 °C); malaise; vomiting; chills; headache; severe backache; possibly accompanied by abdominal pain and/or delirium	Fever decreases from peak levels (approx. 40 °C) and fluctuates throughout this stage; sore throat; enanthem over pharynx; appearance of maculopapular rash first on the face, hands, and forearms (including mouth and pharynx) and subsequently on lower extremities; within days, vesicles form and progress to pustules	General condition improves; scabs form in place of pustules and then separate, leaving depressed, depigmented scars upon healing
S/S Severity	2 (Moderate)	3 (Severe)	CONV

Table 213. SEIRP Model Parameter Values for Smallpox

Parameter	Value
$p_E(X_{Q,n}^{\text{eff}})$ – Infectivity	See Table 210
ρ_S – efficacy of pre-exposure vaccination	0.95
$\rho_E(d)$ – efficacy of post-exposure vaccination	See Table 207
μ_{E1} – minimum duration of incubation period	7 days
μ_{E2} – mean duration of remainder of incubation period	4.6 days
μ_1 – duration of Stage 1	3 days
μ_2 – mean duration of Stage 2	14 days
μ_{RS} – duration of recovery after beginning antibiotics	5 days
α – relative infectiousness	0
$\beta(d)$ – time-varying rate of disease transmission	See *AMedP-7.5* Table 5-85
MT_{I1} – efficacy of medical treatment in Stage 1 of illness	0
$p_f(d)$ – case fatality rate	See Table 209

Note: Fuller explanation of the variables in this table can be found in *AMedP-7.5* Section 5.1.5.

Isolation/Quarantine Model Cohorts and Special Considerations (*AMedP-7.5 Section 5.2.9.3*)

The definitions of the cohorts are sufficiently explained in *AMedP-7.5*. This section explains the equations used to calculate the cohort populations; for definitions of the variables in the equations, see *AMedP-7.5*.

Equation 5-72:	Those who have already finished incubating on the day vaccination is done
Equation 5-73:	Those who are still incubating on the day vaccination is done, minus those for whom vaccination is effective and who therefore do not become ill

1.27. EEEV Disease Model
(*AMedP-7.5 Section 5.2.11*)

Introduction[963]

Eastern equine encephalitis virus (EEEV) is an alphavirus in the *Togaviridae* family. In nature, it is hosted primarily in birds and is transmitted by mosquitoes to horses and humans. Disease caused by EEEV occurs primarily in horses. In humans, infection with EEEV is often asymptomatic. In symptomatic cases, the illness begins as a systemic febrile syndrome referred to as "EEEV disease." In some cases (4%–5% of all EEEV infections according to the Centers for Disease Control and Prevention (CDC)[964]), the virus then invades the central nervous system (CNS), and the disease progresses to what is known as eastern equine encephalitis (EEE), the condition for which the virus is named. With EEE, additional symptoms are caused by inflammation of the brain, and as a result, many survivors have permanent neurological sequelae. Recovery from infection is thought to confer lifelong immunity against reinfection, but it does not confer significant cross-immunity against other alphaviruses (e.g., Western equine encephalitis virus (WEEV) or Venezuelan equine encephalitis virus (VEEV)). Because there is no evidence of direct spread from person to person, we modeled EEEV disease as noncontagious.

EEEV occurs in two antigenically distinct varieties: North American (NA) and South American (SA). The very different transmission cycles of the two varieties have resulted in many human cases caused by, and much investigation into, the NA variety. Far less human data are available on the SA variety due to a lack of evidence for human disease in the regions where the SA variety is prevalent.[965] Although that lack of evidence could simply be a result of underreporting, we assumed that it must be at least due in part to lower virulence in humans. For the human data used in this TRM, we assumed the strain was NA.

All the preceding information is based on the naturally occurring disease, transmitted to a human via mosquito bite. However, the primary threat from EEEV (and VEEV and

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963 This section is largely paraphrased from the following two sources: Keith E. Steele et al., "Alphavirus Encephalitides," chap. 12 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), 241–270; Charles H. Calisher, "Medically Important Arboviruses of the United States and Canada," *Clinical Microbiology Reviews* 7, no. 1 (1994): 89–116. No further citations to them will be made in this section.

964 Centers for Disease Control and Prevention (CDC) Website, "Eastern Equine Encephalitis: Epidemiology & Geographic Distribution," last updated January 26, 2015, http://www.cdc.gov/EasternEquineEncephalitis/tech/epi.html/.

965 Aaron C. Brault et al., "Genetic and Antigenic Diversity among Eastern Equine Encephalitis Viruses from North, Central, and South America," *American Journal of Tropical Medicine and Hygiene* 61, no. 4 (1999): 579.

WEEV) is by aerosol release.[966] Researchers have shown that guinea pigs, mice,[967] and CMs are susceptible to infection by aerosolized EEEV. The authors of the CM study state that "the clinical signs and outcome are similar to mosquito transmission" and that "in both rhesus and cynomolgus macaques, the disease course and severity of clinical signs for the encephalitic alphaviruses (VEE virus, WEE virus, and EEE virus) has in general resembled that of the human infection quite closely."[968]

Given the similarity of NHPs and humans, we assume that the first statement would also be true of humans, and therefore human data from naturally occurring cases may be used to derive the model without negative impact on the model's applicability to scenarios involving aerosolized EEEV. The second statement indicates that NHP data may be considered relevant, although we, of course, prefer human data over NHP data.

Assumptions (*AMedP-7.5 Section 5.2.11.2*)

> **Assumption**: The disease caused by EEEV is independent of the route of exposure (inhalation versus vector-borne).

The introduction explained the reasoning supporting this.

> **Assumption**: The incidence of encephalitic disease resulting from inhalation of EEEV is negligible in military populations; only the nonlethal systemic febrile syndrome (EEEV disease) occurs.

See Subsection 0.

> **Assumption**: The virus is a North American strain.

As mentioned in the introduction, the SA strains appear to be less virulent. Therefore, an enemy who weaponizes this agent would likely choose an NA strain.

Human Response Model (*AMedP-7.5 Tables 5-87 and 5-88*)

Literature Summary

Human Data

Although many published case reports of EEE and a few epidemiological studies on EEE are available, most do not contain information that was useful for developing the

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966 U.S. Army Medical Department Center and School (USAMEDDC&S), *Multiservice Tactics, Techniques, and Procedures for Treatment of Biological Warfare Casualties*, ATP 4-02.84/MCRP 4-11.1C/NTRP 4-02.23/AFMAN 44-156_IP (Washington, DC: U.S. GPO, March 2013), 4-5.

967 Chad J. Roy et al., "Pathogenesis of Aerosolized Eastern Equine Encephalitis Virus Infection in Guinea Pigs," *Virology* 6, no. 1 (2009): 170–182.

968 Douglas S. Reed et al., "Severe Encephalitis in Cynomolgus Macaques Exposed to Aerosolized Eastern Equine Encephalitis Virus." *Journal of Infectious Diseases* 196, no. 3 (2007): 449.

models for this chapter, other than to corroborate the description of symptoms that is more thoroughly given in *MABW* and *MMBC*. Although a few laboratory exposures seem to have occurred, we could not find any details beyond mention that they happened.[969]

One particularly useful paper was part of a series published by Goldfield et al. concerning the 1959 outbreak of EEE in New Jersey. Of the series, the paper[970] of particular use for this chapter discussed the "inapparent infection:disease ratio." We use the Goldfield paper extensively in Subsection 0 to arrive at the important conclusion that *cases of actual encephalitis should be ignored for the purpose of AMedP-7.5*.

The only other paper containing human data that significantly influenced the model derivation is a review of a number of cases by Deresiewicz et al.[971] This paper provided the data used to develop the duration of illness model. The infectivity and incubation period models were derived from the animal data discussed below.

Animal Data

We found reports on mice, guinea pigs, golden hamsters, and three species of NHP challenged with EEEV. Since we had NHP data and, in each case, the authors of the study concluded that their specific type of NHP was a good model of human disease, we used the NHP data and did not use the data from other animal models. The NHP studies are summarized in chronological order in the following paragraphs.

The first paper, published in 1932 by Howitt,[972] discusses intracerebral inoculation of several different animal species, including two RMs. The article focuses on attempts to recover virus from the blood of challenged animals and then describes further experiments only with guinea pigs. It does not contain information that can be used for the development of models for *AMedP-7.5*.

A 1936 report by Hurst[973] describes the results of intradermal (ID), IM, IV, intrasciatic, or intracranial injection of EEEV in RMs. The dose was reported only as a multiple of the "minimum infective dose," so these data could not be used for the infectivity model. Hurst noted that the animals either had an inapparent infection or developed

969 R. P. Hanson et al., "Arbovirus Infections of Laboratory Workers," *Science* 158, no. 3806 (1967): 1284.

970 Martin Goldfield, James N. Welsh, and Bernard F. Taylor, "The 1959 Outbreak of Eastern Encephalitis in New Jersey: 5. The Inapparent Infection:Disease Ratio," *American Journal of Epidemiology* 87, no. 1 (1968): 32–38.

971 Robert L. Deresiewicz et al., "Clinical and Neuroradiographic Manifestations of Eastern Equine Encephalitis," *New England Journal of Medicine* 336, no. 26 (1997): 1867–1874.

972 Beatrice F. Howitt, "Equine Encephalomyelitis," *Journal of Infectious Diseases* 51, no. 3 (1932): 493–510.

973 E. Weston Hurst, "Infection of the Rhesus Monkey (*Macaca mulatta*) and the Guinea-Pig with the Virus of Equine Encephalomyelitis," *Journal of Pathology* 42, no. 1 (1936): 271–302.

encephalitis and, important, *that the route of exposure had no bearing on the likelihood of development of encephalitis.* Further, in his descriptions of symptoms, no correlation with route of exposure is mentioned, suggesting that the route of exposure did not have any effect on symptoms. Some information on the time-course of the disease is presented and is discussed further in the incubation period and duration of illness sections of this chapter.

The next paper was published by Wyckoff and Tesar in 1939.[974] It describes IV or intranasal (IN) inoculation of EEEV, but, again, the dose information cannot be used for the infectivity model for *AMedP-7.5*. The paper echoes Hurst's observation that the route of exposure has little effect on the clinical course. Although much of the paper is devoted to the effects of treatment with immune serum from other animals or from vaccines, some limited information on the clinical course is presented.

The next NHP journal article that we found was published in 1969 by Nathanson, Stolley, and Boolukos.[975] The report describes the inoculation of the RMs in terms of "suckling mouse LD50," so the dose in plaque-forming units (PFU) cannot be determined. The strains are from the brain of a deceased EEE patient and a mosquito pool near the deceased's house. As for details of the clinical course, the report only states that "animals developed severe symptoms on Day 3 or 4 after inoculation, with frequent generalized convulsions and muscle spasm. On Day 4, all monkeys were prostrate on the floor of their cage, with minimal residual muscle power, and were killed."[976] After reviewing the distribution of lesions produced in the monkey CNS and human CNS (from their case and other literature), the authors concluded that they were similar.

A gap in the literature then occurs on NHP infection with EEE. The next article we found was published in 2007 by USAMRIID personnel (Reed et al.).[977] The purpose of the paper is to show that CMs are suitable models of aerosol exposure to EEEV and the resulting disease. The paper provides specific dose-response data, useful for the infectivity model, in addition to clinical course information. These authors also concluded that the disease in NHPs is similar to that in humans and that the clinical signs after aerosol exposure were similar to those after mosquito transmission.

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974 Ralph W. G. Wyckoff and Walter C. Tesar, "Equine Encephalomyelitis in Monkeys," *Journal of Immunology* 37, no. 4 (1939): 329–343.

975 N. Nathanson, P. D. Stolley, and P. J. Boolukos, "Eastern Equine Encephalitis: Distribution of Central Nervous System Lesions in Man and Rhesus Monkey," *Journal of Comparative Pathology* 79, no. 1 (1969): 109–115.

976 Ibid., 111.

977 Reed et al., "Severe Encephalitis in Cynomolgus Macaques."

The next paper, published in 2008 by Adams et al.,[978] describes IN challenge of marmosets with EEEV. It reports the dose given to each animal and some clinical course information. The authors conclude that the marmoset is also a useful model of human EEE for pathogenesis studies and countermeasure efficacy studies.

In a 2009 study with *Aotus nancymaae* owl monkeys by Espinosa et al.,[979] six animals were inoculated subcutaneously, and another six were inoculated intranasally, each with 10^4 PFU of an NA strain. None of the animals exhibited any clinical signs or symptoms of disease, so the data cannot be used for *AMedP-7.5* except potentially for the infectivity model.

Two more papers that focused on safety and efficacy testing of vaccines in CMs were published in 2013 (Roy et al.)[980] and 2014 (Reed et al.).[981] Each study included a number of control animals that were sham-vaccinated and then challenged with a high dose (~10^7 PFU). Roy et al. provide enough information to determine the number of controls that became ill, but Reed et al. do not, so the Reed et al. data cannot be used for the infectivity model. In both cases, the time to symptom onset is not clearly stated. The only clinical course information available in either case is the time to death. We submitted a request to USAMRIID for additional data derived from the controls but did not receive such data in time to include it in the analysis.

One observation from the NHP data is that *regardless of the route of exposure*, progression to encephalitis seems to be the rule, rather than the exception. On the contrary, in natural cases in humans, progression to encephalitis is the exception, rather than the rule (see Subsection 0). Thus, the high incidence of EEE in NHPs challenged by aerosol cannot be used to argue that aerosol exposure is likely to lead to a higher incidence of EEE in humans. In fact, if the NHP data are considered together, these data indicate that route of exposure has little or no effect on the likelihood of progression to EEE.

A further consequence of the preceding paragraph is that animal data must be used carefully. First, any data used for the infectivity model should relate to all animals that

978 A. Paige Adams et al., "Common Marmosets (*Callithrix jacchus*) as a Nonhuman Primate Model to Assess the Virulence of Eastern Equine Encephalitis Virus Strains," *Journal of Virology* 82, no. 18 (2008): 9035–9042.

979 Benjamin J. Espinosa et al., "Susceptibility of the *Aotus nancymaae* Owl Monkey to Eastern Equine Encephalitis," *Vaccine* 27, no. 11 (2009): 1729–1734.

980 Chad J. Roy et al., "A Chimeric Sindbis-Based Vaccine Protects Cynomolgus Macaques against a Lethal Aerosol Challenge of Eastern Equine Encephalitis Virus," *Vaccine* 31, no. 11 (2013): 1464– 1470.

981 Douglas S. Reed et al., "Combined Alphavirus Replicon Particle Vaccine Induces Durable and Cross- Protective Immune Responses against Equine Encephalitis Viruses," *Journal of Virology* 88, no. 20 (2014): 12077–12086.

become ill, regardless of whether the illness progresses to EEE. Similarly, incubation period data must relate to the onset of EEEV disease, not EEE. Finally, any duration of illness data must be sufficiently well described so that there is no ambiguity regarding which stage of disease, or symptoms, the duration data relate to. These issues will be discussed further in the context of specific animal data that are used, where appropriate, in the following sections.

Infectivity

No human data are available that can be used to derive an infectivity model. Thus, we used the available NHP data. Although we have previously discussed the evidence from NHPs that the course of disease does not depend on the route of exposure, we expect that the dose required to produce infection likely does depend on the route of exposure. Since the primary military concern is the use of an aerosol EEEV weapon, data from subcutaneous inoculation are excluded here. IN data are included for discussion, despite uncertainty about the equivalence of these data to inhalation data.

As summarized above, four of the five most recent papers present data that could potentially be used for the infectivity model. Some additional discussion is warranted here to explain the interpretation of the information presented in the papers, as summarized in Table 214.

Table 214. NHP Data Considered for Development of the EEEV Infectivity Model

Source	NHP Species	Challenge Route	Dose (PFU)	Number of NHPs Ill/ Challenged
Reed et al., 2007	CM	Inhalation	3.65×10^6 1.27×10^7	4/6 6/6
Adams et al.	Marmoset	IN	1×10^6	3/3
Espinosa et al.	Owl monkey	IN	1×10^4	0/6
Roy et al., 2013	CM	Inhalation	7.0×10^7	6/6

Note: See Appendix B for full reference citations.

The Reed et al. paper states that two groups of six CMs inhaled one of two aerosol doses of NA strain FL91-4679: either 3.65×10^6 PFU or 1.27×10^7 PFU. All the CMs in the high-dose group died, so it is clear that they all became ill. Four of the low-dose group survived. The article first states that the four survivors "survived challenge with little or no external signs of disease," but later also states that "two of the macaques in the low-dose group that were viremic did develop a fever after exposure but survived."[982] Although viremia alone would not count as "response" for *AMedP-7.5*, the development of a fever

982 Reed et al., "Severe Encephalitis in Cynomolgus Macaques," 444–446.

does count, particularly since the infectivity model is intended to estimate the number of people who will have EEEV disease, not EEE. Thus, Table 214 shows *four* NHPs ill for the Reed et al. low-dose data (two that died and two that developed fever).

Adams et al. states that two groups of three marmosets were challenged intranasally with 1×10^6 PFU. One group was challenged with an NA strain (FL93-393), and all became ill and died. The other group was challenged with an SA strain (BeAr436087) and never even developed fever despite clinically detectable infection. The SA strain data are not included since this strain appears to be avirulent.

Espinosa et al. reported on six owl monkeys inoculated intranasally with 1×10^4 PFU of NA strain FL 93-939. None of the animals exhibited any clinical signs or symptoms.

The six CM controls reported by Roy et al. received a sham vaccination and were subsequently challenged by aerosolized NA strain FL93-939. The dose was reported as $(7.0\pm0.1)\times10^7$ PFU for all animals (the average dose is used in Table 214). For the infectivity model, the uncertainty estimate is removed. All six of the control CMs became ill and died.

The question now is how the Table 214 data should be used. One relevant question is which, if any, species is the best model of humans. There is no obvious answer to that question. Answering the question would require human data. Thus, there is no reasonable basis for choosing one species instead of another. Challenge route is also a consideration. There is no evidence in a single species of whether IN or aerosol inhalation challenge would lead to different ID50 estimates, but given the uncertainty, it seems prudent to choose the aerosol inhalation data since that route of exposure is of primary concern for the military planner. Probit analysis of the Reed et al. and Roy et al. data yields the following estimates for CMs: $ID_{50} = 2.8\times10^6$ PFU (95% CI does not converge, indicating high uncertainty), and PS = 3.8 probits/log (dose) (95% CI 0.0–11.0). Although the uncertainty is obviously quite high, this estimate is the best one available for CMs, given the data.

Now it is important to consider how the CM estimate should be applied to humans. As discussed in Subsection 0, the estimated ID_{50} for VEEV is 10 PFU. However, the VEEV ID_{50} for CMs is 1.33×10^6 PFU,[983] indicating that CMs are resistant to VEEV infection relative to humans. Given the similarity between VEEV and EEEV, it seems wise to assume that CMs are also more resistant to EEEV than humans. Thus, a scaling factor is needed. The only scaling factor available is that indicated by the ratio of the CM VEEV

983 William D. Pratt, Paul Gibbs, M. Louise M. Pitt, and Alan L. Schmaljohn, "Use of Telemetry to Assess Vaccine-Induced Protection Against Parenteral and Aerosol Infections of Venezuelan Equine Encephalitis Virus in Non-Human Primates," *Vaccine* 16, No. 9/10 (1998): 1058.

ID_{50} to the human VEEV ID_{50}s: 1.33×10^6 PFU/10 PFU = 1.33×10^5. Applying this ratio to the CM ID_{50} for EEEV: 2.8×10^6 PFU/1.33×10^5 = 21 PFU. Thus, 21 PFU is the ID_{50} used in *AMedP-7.5* for EEEV. The probit slope of 3.8 probits/log (dose) estimated from the CM EEEV data (see previous paragraph) is also used.

Lethality

This submodel was developed with the understanding, based on reports of historical outbreaks, that only if the disease progresses to EEE is there a chance of the patient dying. That is, nobody dies as a result of EEEV disease alone. Thus, relative to other biological agent models for *AMedP-7.5*, this model will in theory require the extra step of determining what fraction of the ill population (as estimated using the infectivity model) will have EEE, as opposed to having only EEEV disease. Analogous to a case fatality rate, we will discuss this (the distinction between those who have EEEV disease and those who have EEE) in terms of a "case encephalitis rate," or CER. With a CER in hand, a CFR estimate that applies only to the EEE population can then be used. For the CER and the CFR, sufficient human data are available, so we do not discuss animal data here.

Goldfield, Welsh, and Taylor published a journal article discussing what they called the "inapparent infection:disease ratio" in a 1959 outbreak in New Jersey. Since they defined "disease" in their paper as "the occurrence of overt, recognized encephalitis,"[984] their "inapparent" infections include *both* cases of EEEV disease *and* cases of truly subclinical infection. The former must be included in *AMedP-7.5*, and the latter must not be included in *AMedP-7.5*.

Goldfield, Welsh, and Taylor tested the blood of 1,620 people who lived in the area of the outbreak and had never had encephalitis to first determine the approximate percentage of the sampled population that had recent "inapparent" infections. They then used census data to scale up to the full population and estimate an expected number of inapparent infections in various geographical subunits (e.g., towns). Given the known number of overt cases of EEE among residents of each geographical subunit during the outbreak, the authors estimated the inapparent infection:disease ratio. Table 215 is a reproduction of a portion of the table they presented that breaks down the results by age. Having separate estimates by age is important because it is known that the children and the elderly are more likely to suffer encephalitis[985] (as can be seen in Table 215), whereas the military population relevant for *AMedP-7.5* excludes children and the elderly.

Given the data available, the military population is best represented by the ages 15–54. Thus, an additional row (not reported in the original journal article) has been added at

984 Goldfield, Welsh, and Taylor, "The 1959 Outbreak," 32.

985 Steele et al., "Alphavirus Encephalitides," 253.

the end of Table 215 showing that there were 0 overt cases of EEE and 119 expected inapparent infections. As noted previously, the Table 215 data includes both those who had EEEV disease but not EEE and those who had no symptoms whatsoever. This latter population must be excluded before the CER is estimated.

Table 215. Goldfield, Welsh, and Taylor Data on Age-Related Data Relevant to CER

Age	Census Population	Expected # of Inapparent Infections in Population	Number of Overt Cases	Inapparent infection: disease ratio
0–4	1,274	41	5	8
5–14	2,061	52	2	26
15–24	1,315	17	0	>17
25–34	1,421	47	0	>47
35–44	1,423	30	0	>30
45–54	1,471	25	0	>25
55+	2,922	79	5	16
All	11,877	271	12	23
15–54[a]	5,630	119	0	>119

[a] This row was not included in the original article.

Fortunately, Goldfield, Welsh, and Taylor also reported that 59% of those detected to have had a recent EEEV infection "claimed to suffer some affection"[986] during the outbreak, whereas the background level of such claims in those *not* detected to have had a recent EEEV infection was 11%. One can thus estimate that during the 1959 outbreak, about 48% of the population suffered EEEV disease. Thus, a reasonable estimate of the number of people who had EEEV disease but not EEE during the 1959 outbreak is $0.48 \times 119 \approx 57$. Thus, the estimated CER based on the 1959 outbreak is something less than 100%/57 = 1.75%.

One final consideration is whether the CER derived from natural outbreak data is relevant for aerosol exposure. As noted in Subsection 0, Hurst stated that based on ID, IM, IV, intrasciatic, and intracranial injections in RMs, the route of exposure had no bearing on the likelihood of development of encephalitis. His conclusion is based on tests with at least 20 RMs; however, since the actual number of RMs used is not clear, the degree of confidence in his conclusion is also not clear. Regardless, no other data are available to estimate the CER, so we have no choice but to use the CER estimate derived in the previous paragraph.

986 Goldfield, Welsh, and Taylor, "The 1959 Outbreak," 35.

Since the final CER estimate is rather low—only 1.8%—and the CFR would apply only to that 1.8%, it is worth considering whether cases of EEE and the resulting fatalities should be considered at all in *AMedP-7.5*. The CDC estimates a CFR of 33%,[987] which would mean that only 0.6% of the total ill (as indicated by the infectivity model) would be estimated to die. One of the assumptions of *AMedP-7.5* is that CFRs less than 1% are considered negligible (see Subsection 0 of this TRM) because they will have so little effect on the results and the related planning. For the same reason, the incidence of EEE, in general, will be ignored, which also means that the model will use a 0% CFR since EEEV disease alone does not cause fatalities.

Incubation Period

Before discussing the data used for the model, we must again consider the difference between EEEV disease and EEE. Since EEEV disease occurs first chronologically, any data used for the incubation period model must clearly refer to the first onset of symptoms, not the onset of encephalitis (particularly since encephalitis is actually excluded from the model, per Subsection 0).

We first turn to animal data to answer the question of whether the incubation period depends on the route of exposure, specifically in terms of aerosol exposure. Animal data are required because there are no known data relating to human aerosol exposure.

The NHP data available for conducting this comparison are somewhat sparse (see Table 216) but probably sufficient. In only one of the datasets is it unclear whether the onset of symptoms is meant to refer to EEEV disease or EEE—the Nathanson, Stolley, and Boolukos data. Otherwise, the first symptom is fever, which is a symptom of EEEV disease. The most recent two NHP journal articles (Roy et al. 2013 and Reed et al. 2014) do not provide any information on the incubation period.

Although no statistical test suggests itself for the Table 216 data, there appears to be no difference in the incubation period as a function of route of exposure. One of Hurst's purposes was to discover how the route of exposure affected the clinical course, and he made no comments on it affecting incubation. Further, the numbers line up rather well, including for the comparison of aerosol inhalation to all other data. Based on Table 216, we conclude that the incubation period in NHPs does not depend on route of exposure, and we assume that the same is true in humans. Thus, data from naturally occurring human cases are relevant.

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987 Centers for Disease Control and Prevention (CDC) Webstie, "Eastern Equine Encephalitis," last updatged August 16, 2010, http://www.cdc.gov/easternequineencephalitis/.

Table 216. NHP Incubation Period Does Not Depend on Route of Exposure

Source	NHP Species	Route of Exposure	Incubation Period (days)
Hurst	RM	ID, IM, IV, intrasciatic, intracranial	Between 3 and 9 (n > 20, total not clear); no discussion of dependence on route
Wyckoff and Tesar	RM	IN, intralingual	About 3 days (n > 7, total not clear)
Nathanson, Stolley, and Boolukos	RM	Intracranial	3 (n = 3), 4 (n = 1)[a]
Reed et al., 2007	CM	Inhalation	3 (n = 5), 4 (n = 1), 5.5 (n = 1), and 7.5 (n = 1)
Adams et al.	Marmoset	IN	2–4

Note: See Appendix B for full reference citations.

[a] In this case, it is unclear whether the incubation period information in the article refers to the onset of EEEV disease or the onset of EEE.

Although many articles provide information on historical outbreaks, in most cases, they do not provide information on the incubation period. This omission is not surprising, since few people can recall the exact day that they were bitten by a mosquito, and they may have been bitten by a mosquito on many days leading up to the onset of their illness. A further complication is that most historical literature has focused on EEE, not EEEV disease. One database that specifically identified the "prodrome" before encephalitis systems was created by Deresiewicz et al.,[988] but it no longer exists.[989]

The only human incubation period data that we found are as follows. A study of 16 cases of EEE in Massachusetts[990] provides information on incubation period for one case, stating that the individual was camping in the *presumed* area of exposure 2 weeks before hospital admission and became ill (fatigue, fever, myalgia) 1 week before admission—an incubation period of 1 week. The CDC reports that the "time from infected mosquito bite to onset of illness" in humans is 4 to 10 days.[991] *MABW* states, "The incubation period in humans varies from 5 to 15 days,"[992] and immediately afterward discusses the febrile

988 Deresiewicz et al., "Clinical and Neuroradiographic Manifestations."

989 IDA contacted Dr. Deresiewicz to request his database. He reported that detailed data had been collected via contacts with patients and hospital; however, the original dataset was lost in a computer malfunction, and no hard copies of the spreadsheets could be located.

990 M. M. Przelomski et al., "Eastern Equine Encephalitis in Massachusetts: A Report of 16 Cases, 1970-1984," *Neurology* 38, no. 5 (1988): 736–739, 736.

991 Centers for Disease Control and Prevention (CDC) Website, "Eastern Equine Encephalitis Symptoms & Treatment," last updated August 16, 2010. http://www.cdc.gov/EasternEquineEncephalitis/tech/symptoms.html.

992 Steele et al., "Alphavirus Encephalitides," 253.

prodrome. Thus, it is clear that these latter two sources are referring to the onset of EEEV disease, not EEE. The problem, however, is that neither provides a reference for their statement, and given the lack of data in the literature, it seems that these must be simply best guesses by the authors.

Given the lack of human data, we turn back to the NHP data despite the relatively short incubation periods compared with those given in statements by the CDC and *MABW*. Although we previously argued that route of exposure does not appear to affect the incubation period, we admit some uncertainty and therefore chose to use the Reed et al. data—the only inhalation data available—to derive the incubation period submodel. Of the eight CMs that became ill, the onset of fever occurred after 3 days for five CMs, 4 days for another, 5.5 days for another, and 7.5 days for another. The arithmetic mean and standard deviation from these data are 4.0 and 1.7 days, respectively. Since the supporting data for EEE incubation do not indicate any particular type of distribution, we chose a lognormal because it is somewhat "the standard" for *AMedP-7.5*. As noted, this distribution is shorter than the CDC and *MABW* statements, but we prefer it because it is based on traceable data, whereas the provenance of the CDC and *MABW* estimates is unknown, and the estimates appear to be guesses.

Injury Profile

A reminder of the findings from Subsections 0 and 0 is warranted before discussing the Injury Profile. These findings were as follows:

- In NHPs, the route of exposure has no bearing on the likelihood of development of EEE as a follow-on to EEEV disease.
- In humans, the CER is approximately 1.8% for naturally occurring cases, which is sufficiently small that EEE need not be considered for *AMedP-7.5*, which is a planning tool.

Assuming that the first point is also true in humans, the conclusion to be drawn from these two points is that the Injury Profile (and duration of illness) submodels should only cover EEEV disease. EEE is specifically excluded. With this in mind, the following CDC statement is relevant:

> EEEV infection can result in one of two types of illness, systemic or encephalitic (involving swelling of the brain, referred to below as EEE). The type of illness will depend on the age of the person and other host factors. It is possible that some people who become infected with EEEV may be asymptomatic (will not develop any symptoms).

> Systemic infection has an abrupt onset and is characterized by chills, fever, malaise, arthralgia, and myalgia. The illness lasts 1 to 2 weeks, and recovery is complete when there is no central nervous system involvement.[993]

Similarly, the following statement is the relevant excerpt from Deresiewicz et al.'s report on 36 cases of EEE (including investigation into the patients' recent histories):

> For most patients, the illness began with a short prodrome (median, 5.0 days; range, 0 to 28), typically mimicking a benign viral illness; fever, headache, and abdominal distress were common.[994]

Table 217 shows the Injury Profile for EEEV disease: a single stage with flu-like symptoms, followed by recovery. If EEE had been included in the model, additional stages would have been required. Injury Severity Level 2 (Moderate) was chosen because in most historical cases, people did not report to the hospital until the onset of encephalitis (so Injury Severity Level 3 would be inappropriate—see Table 2), and the symptoms definitely seem worse than Mild.

Table 217. EEEV Disease Injury Profile

	Stage 1
S/S	Fever; headache; nausea and vomiting; malaise and weakness; arthralgia; myalgia
S/S Severity	2 (Moderate)

Duration of Illness

Again, the reminder that the model will only include EEEV disease, not EEE, is important. For the duration of illness submodel, not including EEE severely limits the pool of data from which a model can be derived. Since most cases of EEEV infection are only recognized as such upon the onset of EEE, most of the literature focuses on EEE, not on EEEV disease. In fact, while we were able to find some information relating to the length of EEEV disease as a prodrome to EEE, we did not find any data describing EEEV disease that did not lead to EEE, and it is not clear whether the former should be thought of as equivalent to the latter. Unfortunately, the NHP data from the references cited in Section 0 make it clear that NHPs progress through the disease much faster than humans, regardless of exposure route, so the NHP data cannot be used.

Two statements, again from the CDC and *MABW*, provide a starting point for considering the length of EEEV disease. In describing the "systemic infection," the CDC

993 Centers for Disease Control and Prevention (CDC) Website, "Eastern Equine Encephalitis Symptoms & Treatment."

994 Deresiewicz et al., "Clinical and Neuroradiographic Manifestations," 1868.

says "the illness lasts 1 to 2 weeks."[995] *MABW* says that the "febrile prodrome" lasts up to 11 days before the onset of neurological disease.[996] *MABW* also says that viremia is detectable during the febrile "prodrome" to EEE but is *not* detectable by the time clinical encephalitis develops.[997] There is some gap in time between the disappearance of detectable viremia and the onset of EEE, which means that we cannot correlate the disappearance of viremia with the end of EEEV disease symptoms, and therefore it is also not strictly correct to use the reported prodromes before EEE to model the length of EEEV disease. However, the only data available related to the duration of EEEV disease *do* relate to the prodromes before EEE, and we therefore *must* use them if we are to create a model, despite the uncertainty related to a model derived using such a tactic. Those data are presented in the following paragraphs.

Przelomski et al. report that in Massachusetts between 1970 and 1984, illness duration was age-dependent. Three patients (implied but not actually stated to have been under 10 years of age) had prodromes of 1 to 4 days or none at all, whereas 9 of 11 older patients had prodromes of 5 to 7 days.[998]

The only other dataset that we found comes from a review of the records of 36 patients[999] by Dr. Deresiewicz's team. The report says that the median prodrome[1000] duration was 5 days, with a range of 0 to 28.[1001] Other information is also provided, but since it relates to EEE, it is not useful here. This description is consistent with the CDC statement, the *MABW* statement, and the few data points from Przelomski et al. Since Deresiewicz et al. did not publish the underlying data, their data could not be combined with the Przelomski data to make a larger dataset. We chose to use the largest dataset available—that from Deresiewicz et al.

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995 Centers for Disease Control and Prevention (CDC) Website, "Eastern Equine Encephalitis Symptoms & Treatment."

996 Steele et al., "Alphavirus Encephalitides," 253.

997 Ibid.

998 Przelomski et al., "Eastern Equine Encephalitis in Massachusetts," 737.

999 Dr. Deresiewicz's team reviewed the records from all cases of EEE reported in the United States between 1988 and 1994.

1000 The paper defines prodrome as "the period between onset of symptoms that were reasonably attributable to eastern equine encephalitis and the first major neurologic manifestation (altered mental status, seizure, hemiparesis, or severe headache and a temperature of at least 103°F)." (See Deresiewicz et al., "Clinical and Neuroradiographic Manifestations," 1868.) This definition is consistent with treating the prodrome as EEEV disease.

1001 Deresiewicz et al., "Clinical and Neuroradiographic Manifestations," 1868.

As was the case with melioidosis (Subsection 0), the best type of distribution to fit the format of the available data is a PERT distribution.[1002] However, while a minimum of *zero* days makes sense for a prodrome to EEE (the onset of encephalitis coincided with the onset of symptoms in general), we arbitrarily modified the minimum to 1 day so that the model will not predict somebody recovering in 0 days.[1003] Using a minimum of 1 day, a maximum of 28 days, and a median of 5 days, the PERT parameters presented in Table 218 can be calculated.

Table 218. PERT Parameters for EEEV Disease Duration of Illness Model

	Stage 1
Minimum	1
Maximum	28
Median	5
PERT mean (μ)[a]	8.2
PERT parameter 1 (α)[a]	1.6
PERT parameter 2 (β)[a]	4.4

[a] Calculated from the minimum, maximum, and median.

Medical Countermeasures and Treatment Model

The only available treatment for EEEV disease is palliative care.[1004] There are no vaccines or drugs available to prevent or treat EEEV disease (though there is ongoing research on vaccine development). Therefore, there are no EEEV disease treated submodels.

Model Summary

Table 219 and Table 220 summarize the model parameters for EEEV disease used in *AMedP-7.5*. Note that EEE—the disease involving the actual encephalitis for which the virus is named—is *excluded* from the model (per Subsection 0). While the parameters in these tables represent current best estimates, any new data that become available, particularly human data related to incubation period or duration of illness, would likely improve the model.

[1002] One could also choose a triangle distribution, but our preference is PERT. Our choice is arbitrary.

[1003] This problem reinforces to the idea that it would be best *not* to use the prodrome data to model the duration of EEEV disease. However, as stated previously, no other data are available.

[1004] Steele et al., "Alphavirus Encephalitides," 255.

Table 219. EEEV Disease Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 21 PFU Probit slope = 3.8 probits/log (dose)
Lethality[a]	Rate	0%
Incubation period	Lognormal distribution	Mean = 4.0 days Standard deviation = 1.7 days μ = 1.303; σ = 0.407
Duration of illness	PERT distribution	Minimum = 1 day Median = 5 days Maximum = 28 days μ = 8.2; α = 1.6; β = 4.4

[a] The same rate is used for the "case encephalitis rate."

Table 220. EEEV Disease Injury Profile

	Stage 1
S/S	Fever; headache; nausea and vomiting; malaise and weakness
S/S Severity	2 (Moderate)

Cohorts and Special Considerations (*AMedP-7.5 Section 5.2.11.3*)

Cohort populations are calculated according to the standard equations for E, F, and S in *AMedP-7.5*; no further explanation is warranted.

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1.28. VEEV Disease Model
(*AMedP-7.5 Section 5.2.12*)

Introduction

Venezuelan equine encephalitis (VEE) virus (VEEV) is an alphavirus, one of four genera making up the *Togaviridae* family. The natural hosts of the virus are equines and rodents, and the virus is transmitted by arthropod vectors such as ticks, fleas, or mosquitoes. Epizootic and enzootic strains of VEEV can be found in nature, and both cause disease in humans.[1005] Although there have been several large outbreaks in the past, immunization is now common for equines of all types throughout North and South America.[1006]

Humans are highly susceptible to infection with VEEV. While commonly spread by mosquitoes, experience with the virus in the laboratory has shown it to be highly infectious via aerosol: VEEV is responsible for more laboratory-acquired disease than any other arbovirus.[1007] Because so many laboratory-acquired infections have occurred and such cases are either presumed or known to be the result of inhalation of VEEV aerosol, there was no need to use data from natural (vector-driven) outbreaks or cases to derive the model or to rely on animal data for the models.

Unlike EEEV and WEEV, essentially all human infections with VEEV are symptomatic.[1008] However, naturally occurring (spread by vector) VEEV is similar to EEEV and WEEV in that the "case encephalitis rate" is very low in adults—"in one epidemic, the ratio of encephalitis to infections was estimated at less than 0.5% in adults."[1009] We assume the same is true for cases caused by inhalation of VEEV. Thus, this model is for VEEV disease, which is the systemic febrile syndrome, not VEE, which includes encephalitis.

Some final caveats: (1) because there is no evidence that the virus can be directly spread from person to person, we modeled VEEV disease as a noncontagious disease; (2) all subtypes of VEEV are assumed to result in a similar disease progression for the purpose deriving a human response model for *AMedP-7.5*; (3) for the purpose of estimating the CFR and for determining the severity of the disease as indicated by the Injury Profile, we assumed that different routes of exposure produce similar results.

[1005] Steele et al., "Alphavirus Encephalitides," 242.
[1006] Ibid., 248.
[1007] Ibid., 242.
[1008] Ibid., 252.
[1009] Ibid., 252.

Assumption (*AMedP-7.5 Section 5.2.12.2*)

> **Assumption**: The incidence of encephalitic disease resulting from inhalation of VEEV is negligible in military populations; only the nonlethal systemic febrile syndrome (VEEV disease) occurs.

The introduction provides sufficient explanation.

Human Response Model (*AMedP-7.5 Tables 5-91 and 5-92*)

Infectivity

Many accidental laboratory-acquired infections have occurred,[1010] indicating that the infectious dose is rather low. Contrasting that is the VEEV ID_{50} for CMs, 1.33×10^{6} PFU,[1011] which is a very high dose. Thus, NHPs data are not suitable for estimating the human ID_{50}. We are not aware of any animal model that has been determined to be suitable for estimating the human ID_{50}. Since there are no human data, we are left with an SME estimate of 10 PFU. The idea behind this estimate is that probably only 1 PFU *retained* is necessary to establish an infection, but the fraction of what is inhaled that is retained may be as low as 10%.

Although the SME estimate is for the ID_{50}, it was implemented in *AMedP-8*(*C*) using a threshold model because there is no associated SME estimate of the probit slope. For *AMedP-8*(*C*) the assumption was made that "all inhaled agent is retained"[1012] in the lungs, and on that basis it used a threshold of 1 PFU.

Since *AMedP-7.5* does not include the assumption that all inhaled agent is retained, it instead uses a threshold of 10 PFU. This corresponds better to the other infectivity models, the underlying data for which reflect the amount of agent *inhaled*, not the amount retained. Thus, the 10 PFU estimate of the ID_{50} is also suitable for use to estimate the EEEV and WEEV infectivities as described in Subsections 0 and 0.

Lethality

As discussed in the introduction, for cases occurring as a result of transmission from a vector, "in one epidemic, the ratio of encephalitis to infections was estimated at less than 0.5% in adults."[1013] *MABW* states that in adult encephalitis cases the fatality rate is 10% and cites an article that does not seem to provide the cited information;[1014] rather, the article, which describes an outbreak in Texas in 1971, shows that there were 47 cases in

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[1010] Steele et al., "Alphavirus Encephalitides," 242.

[1011] Pratt, Gibbs, Pitt, and Schmaljohn, "Use of Telemetry to Assess Vaccine-Induced Protection," 1058.

[1012] NATO, *AMedP-8*(*C*), 1-12.

[1013] Steele et al., "Alphavirus Encephalitides," 252.

[1014] Ibid.

adults aged 20 to 59 and does not mention any deaths but rather discusses the *lack* of deaths observed.[1015] In either case, it is clear that the CFR is so low that it can safely be set to zero for the purpose of *AMedP-7.5*.

Incubation Period

Data for the length of the incubation period for inhalational VEEV disease were collected from published case reviews of accidental laboratory infections. A total of 36 incubation period data points (see Table 221) was used in an MLE analysis to estimate a distribution that would best fit this data.

Table 221. Human Inhalational VEEV Disease Incubation Period Data

Source	# of People	Date of Exposure	Date of Symptom Onset	Incubation Period (days)
Koprowski & Cox	3	1-Feb[a]	2-Feb	1
	1	1-Feb[a]	3-Feb	2
Lennette and Koprowski	1	28-Jun[a]	30-Jun	2
	1	28-Jun[a]	1-Jul	3
	3	28-Jun[a]	2-Jul	4
	1	28-Jun[a]	5-Jul	7
	1	12-Jul[a]	13-Jul	1
	1	12-Jul[a]	14-Jul	2
Slepushkin	15	31-May	1-Jun	1
	7	31-May	2-Jun	2
	2	31-May	4-Jun	4

Note: See Appendix B for full reference citations.

[a] Date of exposure assumed by IDA based on indications in the source.

An analysis of the Table 221 data was conducted using @RISK software[1016] with the chi-squared test of goodness-of-fit, and the best distribution indicated by the software was a Weibull distribution with a mean and standard deviation of 1.94 and 1.24 days, respectively (α = 1.60; β = 2.16).

Other articles were reviewed,[1017] and 98 human cases were disregarded because they were naturally occurring human cases and no precise data existed to indicate the time of

[1015] G. Stephen Bowen, Thomas R Fashinell, Paul B Dean, and Michael B. Gregg, "Clinical Aspects of Human Venezuelan Equine Encephalitis in Texas," *Bulletin of the Pan American Health Organization* 10, No. 1 (1976): Table 1 and 54.

[1016] *@Risk for Excel*.

[1017] William H. Dietz, Pauline H. Peralta, and Karl M. Johnson, "Ten Clinical Cases of Human Infection with Venezuelan Equine Encephalomyelitis Virus, Subtype I-D," *American Journal of*

exposure. Although we did have to estimate times of exposure for some laboratory data, there is less uncertainty with these estimates.

Injury Profile

As a reminder, this chapter addresses VEEV disease, which does not involve encephalitis. Onset of illness is sudden, and prostration is typical. Patients experience high fever, chills, throbbing headache, and malaise. Photophobia, sore throat, myalgia, and vomiting are common. After a period of 2 to 3 days, symptoms abate and patients begin to recover. Mild headache, fatigability, and weakness persist for about a week.[1018] Based on *MABW* and some published case descriptions, we developed the Injury Profile shown in Table 222.

Table 222. VEEV Disease Injury Profile

	Stage 1	Stage 2	Stage 3
Signs and symptoms (S/S)	Malaise, throbbing headache, high fever, chills, night sweats, generalized severe myalgia, severe pain in calf muscles, weakness, anorexia, insomnia, sore throat, photophobia	Generalized weakness, mild headache, mild generalized myalgia, mild fever, mild photophobia, anorexia, insomnia	Generalized weakness, easily fatigued, mild headache
S/S Severity	3 (Severe)	2 (Moderate)	1 (Mild)

Duration of Illness

Three literature sources provided summaries of accidental human inhalation cases, including enough detail to estimate the duration of the three stages of illness. Table 223 shows the information we extracted from the source articles; some interpretation was required.

Table 223. Human Inhalational VEEV Disease Duration of Illness Data

Source	Severe Days (Stage 1)	Moderate Days (Stage 2)	Mild Days (Stage 3)	Total Illness Days
Casals, Curnen, and Thomas	2	2	3	7
	2	1	2	5
Koprowski & Cox	2	4	6	12
	2	3	9	14
	2	3	5	10
	2	10	13	25

Tropical Medicine and Hygiene 28, no.2 (1979): 329–334; Bowen, Fashinell, Dean, and Gregg, “Clinical Aspects of Human Venezuelan Equine Encephalitis in Texas.”

[1018] Steele et al., “Alphavirus Encephalitides,” 252.

	2	5	2	9
	2	2	4	8
	2	3	5	10
Lennette and Koprowski	3	1	1	5
	2	2	2	6
	2	1	2	5
	3	3	5	11
	3	9	8	20

Note: See Appendix B for full reference citations.

Using the @RISK software[1019] to perform fits we derived the following duration of illness model. Stage 1 is modeled as a discrete distribution, with an 80% probability of a 2-day duration and a 20% probability of a 3-day duration. Stages 2 and 3 are both modeled with a lognormal distribution. For Stage 2 the mean and standard deviation are 3.47 days and 2.80 days (μ = 0.993; σ = 0.708), and for Stage 3 the mean and standard deviation are 4.84 days and 3.81 days (μ = 1.336; σ = 0.694).

Medical Countermeasures and Treatment Model

The only available treatment for VEEV disease is palliative care.[1020] Two VEE vaccines were developed by USAMRIID to protect at-risk laboratory and field personnel: a live attenuated vaccine, TC-83, and an inactivated vaccine, C-84.

Over 6,000 people received the TC-83 vaccine from 1965 to 1972. In approximately 20% of cases, vaccinated individuals failed to generate a minimum neutralizing antibody response and were therefore considered unprotected. In another 25% of cases, individuals experienced clinical reactions of sufficient severity to require bed rest. To overcome these disadvantages, the C-84 vaccine was developed. But animal tests of this vaccine led to concerns that it did not protect against aerosol challenge, and it is currently administered only as a booster immunogen.[1021]

At present these vaccines are available as INDs and are not generally available for widespread use. Efforts are ongoing to develop improved vaccines, with particular focus on a trivalent vaccine for EEEV, VEEV, and WEEV. Given the current status of medical countermeasures, however, there are no VEEV disease treated submodels.

[1019] *@Risk for Excel.*

[1020] Steele et al., “Alphavirus Encephalitides,” 255.

[1021] Steele et al., “Alphavirus Encephalitides,” 257–258.

Model Summary

Table 224 and Table 225 summarize the model parameters for VEEV disease used in *AMedP-7.5*. Note that VEE—the disease involving the actual encephalitis for which the virus is named—is *excluded* from the model. While the parameters in these tables represent current best estimates, any new data that become available, particularly human data related to incubation period or duration of illness (since the number of data points underlying the current models is not large), or infectivity data from an animal model shown to be a good model of humans for this purpose, would likely improve the model.

Table 224. VEEV Disease Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Threshold	10 PFU
Lethality	Rate	0%
Incubation period	Weibull distribution	Mean = 1.94 days Standard deviation = 1.24 days α = 1.60; β = 2.16
Duration of illness		
• Stage 1	Discrete	80%: 2 days 20%: 3 days
• Stage 2	Lognormal distribution	Mean = 3.47 days Standard deviation = 2.80 days μ = 0.993; σ = 0.708
• Stage 3	Lognormal distribution	Mean = 4.84 days Standard deviation = 3.81 days μ = 1.336; σ = 0.694

Table 225. VEEV Disease Injury Profile

	Stage 1	Stage 2	Stage 3
Signs and symptoms (S/S)	Malaise, throbbing headache, high fever, chills, night sweats, generalized severe myalgia, severe pain in calf muscles, weakness, anorexia, insomnia, sore throat, photophobia	Generalized weakness, mild headache, mild generalized myalgia, mild fever, mild photophobia, anorexia, insomnia	Generalized weakness, easily fatigued, mild headache
S/S Severity	3 (Severe)	2 (Moderate)	1 (Mild)

Cohorts and Special Considerations (*AMedP-7.5 Section 5.2.12.3*)

Cohort populations are calculated according to the standard equations for E, F, and S in *AMedP-7.5*; no further explanation is warranted.

1.29. WEEV Disease Model (*AMedP-7.5 Section 5.2.13*)

Introduction[1022]

WEEV is similar to EEEV in many ways. Both are an alphavirus; both are hosted primarily in birds and transmitted by mosquitoes to horses and humans; both exist in North and South America; and, most important for this chapter, symptomatic infections with both cause a systemic febrile syndrome (EEEV disease or WEEV disease) that *may* be followed by an encephalitic syndrome (EEE or WEE). Significantly, it is known that in naturally occurring cases, WEEV is less neuroinvasive than EEEV and less likely to lead to death even in cases of neuroinvasion, but it otherwise has a similar pathology.[1023]

Clinical symptoms of WEEV disease are similar to those for EEEV disease: fever, headache, nausea and vomiting, and malaise and weakness. Many strains of WEE exist, but we did not find any indication in the literature of which strains are more virulent for humans, so we did not attempt to account for varying virulence among strains. Accounting for this variance would have been exceedingly difficult since the strain is not reported in human case reports. Since no evidence exists that WEEV disease spreads person to person, we modeled it as a noncontagious disease.

Assumptions (*AMedP-7.5 Section 5.2.13.2*)

> **Assumption**: The disease caused by WEEV is independent of the route of exposure (inhalation versus vector-borne).

The introduction explained the reasoning supporting this.

> **Assumption**: The incidence of encephalitic disease resulting from inhalation of WEEV is negligible in military populations; only the nonlethal systemic febrile syndrome (WEEV disease) occurs.

The introduction and Subsection 0 provide sufficient explanation.

> **Assumption**: All strains can be represented by a single set of model parameter values.

This is a necessity because many of the research articles from which data used to develop the models in this chapter were pulled do not state which strain of WEEV was used.

1022 This section is largely paraphrased from the following two sources: Steele et al., "Alphavirus Encephalitides"; Calisher, "Medically Important Arboviruses."

1023 W. C. Reeves et al., *Epidemiology of the Arthropod-Borne Viral Encephalitides in Kern County, California 1943-1952*, vol. IV of University of California Publications in Public Health. Berkeley, CA: University of California Press, 1962.

Human Response Model (*AMedP-7.5 Tables 5-97 and 5-98*)

Literature Summary

Human Data

Although there are many published case reports of WEE and a few epidemiological studies, most do not contain information that was useful for developing the models for this chapter, other than to corroborate the description of symptoms that is more thoroughly given in *MABW* and *MMBC*. The few sources that did provide information useful for the derivation of the duration of illness model are cited in that section. Three case histories for laboratory-associated cases were also useful for the incubation period and duration of illness models and are cited later.

As with EEEV, the primary threat from is by aerosol release.[1024] Reports of accidental human laboratory infections heighten this concern for WEEV, particularly in light of summary reports that 2 of 5 cases led to death (apparent 40% CFR),[429] or that 4 of 16 cases led to death (apparent 25% CFR).[430] That heightened concern appears to be based on the assumption that the route of exposure in these cases was aerosol, but the summary reports cited do not provide details on the route of exposure. We were able to locate only three case reports of laboratory-caused WEEV infections. Two of the three case reports stated that the infection was most likely caused by the worker being spattered with infected chick embryo (not really an aerosol),[1025] while the route of exposure in the other case report was unknown.[1026] It seems just as likely that these cases were not inhalational and the fact that the patients developed encephalitis is coincidental.

Further, there is the unaddressed issue of the potential number of laboratory-caused illnesses resulting from WEEV exposure that go undetected because the illness manifests as WEEV disease, not as WEE. Given the anecdotal nature of the reporting and the reasons for doubt, it seems that the evidence from human data is insufficient to conclude that aerosol exposure is more likely to cause WEE than natural exposure.

Animal Data

Two of the older NHP studies discussed in the previous chapter also reported on some experiments with WEEV.[1027] However, in each case, far less information related to WEEV

[1024] USAMEDDC&S, *Procedures for Treatment of Biological Warfare Casualties*, 4-5.

[1025] Ferdinand C Helwig, "Western Equine Encephalomyelitis Following Accidental Inoculation with Chick Embryo Virus," *Journal of American Medical Association* 115, no. 4 (1940): 291–292; Herman Gold and Bettylee Hampil, "Equine Encephalomyelitis in a Laboratory Technician with Recovery," *Annals of Internal Medicine* 16, no. 3 (1942): 556–569.

[1026] L. D. Fothergill, Margaret Holden, and Ralph W. G. Wyckoff, "Western Equine Encephalitis in a Laboratory Worker," *Journal of American Medical Association* 113, no. 3 (1939): 206–207.

[1027] Wyckoff and Tesar, "Equine Encephalomyelitis in Monkeys"; Hurst, "Infection of the Rhesus Monkey."

is presented, so much so that the reports do not provide any assistance in developing the specific WEEV disease model for this chapter. What they do make clear is that in RMs, regardless of route of exposure, the disease typically includes encephalitis.

The next report we found involving exposure of NHPs to WEEV was a 2005 paper by Reed et al. on exposing CMs to WEEV aerosols to determine whether CMs were a suitable model of the resulting disease.[1028] The paper provides dose-response data and clinical course information and concludes that the CM is a useful model for evaluating vaccines and therapeutics.

The final report, published in 2014, is also by Reed et al.[1029] It describes safety and efficacy testing of alphavirus vaccines in CMs. The information that the paper provides on the controls is sufficiently vague so that it is not useful for *AMedP-7.5*. We submitted a request to USAMRIID for additional data derived from the controls but did not receive such data in time to include them in the analysis.

Given the above, it is clear that NHPs are susceptible to infection by aerosolized WEEV. In the 2005 report, Reed et al. argue that aerosol exposure is more likely to lead to neuroinvasion because the virus can travel up the olfactory nerves directly to the brain,[1030] but their argument is based on their inability to detect virus in the blood during the course of infection. It is not clear whether the same phenomenon would be observed after other routes of infection. The older articles[1031] describing NHP experiments with other routes of exposure do not comment on attempts to measure virus in the blood nor could we find any other reports of NHP testing with other routes of exposure, so no direct comparison can be made. However, the older articles do provide evidence that in NHPs, progression to encephalitis is the rule, rather than the exception, *even for non-aerosol exposures*.

Thus, the high incidence of WEE in NHPs challenged by aerosol cannot be used to argue that aerosol exposure is likely to lead to a higher incidence of WEE in humans. We admit that the data are less sufficient for WEEV than they were for EEEV and that there is some possibility that aerosol exposure to WEEV is more likely to lead to neuroinvasion than exposure by other routes. No human aerosol data are available, however, and we found only one study that provides usable NHP aerosol data. Creating a model based on aerosol

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[1028] Reed et al., "Aerosol Exposure to Western Equine Encephalitis Virus Causes Fever and Encephalitis in Cynomolgus Macaques," *Journal of Infectious Diseases* 192, no. 7 (2005): 1173–1182

[1029] Reed et al., "Combined Alphavirus Replicon Particle Vaccine."

[1030] Reed et al., "Aerosol Exposure to Western Equine Encephalitis Virus," 1181.

[1031] Wyckoff and Tesar, "Equine Encephalomyelitis in Monkeys"; Hurst, "Infection of the Rhesus Monkey."

data would therefore be impossible. We assumed that the resulting disease does *not* depend on the route of exposure and that data from natural outbreaks are therefore relevant.

Consistent with that assumption and with the low likelihood of neuroinvasion from naturally occurring infections, we will not discuss WEE further except for reminders that it is not considered in this chapter; rather, WEEV disease is considered. These reminders are included because we recognize that this decision will be surprising to most readers.

Infectivity

We did not find any data that could be used to estimate the ID_{50} for humans by percutaneous inoculation. Although we found three case studies of laboratory-acquired infections, the data presented in the reports are inadequate to draw any inferences regarding the infectivity. Further, most of the NHP studies provide no usable information on infectivity.

Although we assumed above that the course of disease is not affected by the route of exposure, we expect that the dose required to produce an infection does depend on the route of exposure. Since the primary military concern is use of an aerosol WEEV weapon, only aerosol data are included here. Further, since NHP aerosol challenge data are available, data from other animal models were not considered.

The only report with usable NHP aerosol challenge data is Reed et al., which shows that six CMs inhaled "6.3±0.5 $\log_{10}$ PFU"[1032] and another six CMs inhaled "7.3±0.4 $\log_{10}$ PFU,"[1033] which we interpret to mean $10^{6.3\pm0.5}$ PFU and $10^{7.3\pm0.4}$ PFU,[1034] respectively. Ignoring the error bars, these doses become 2×10^6 PFU and 2×10^7 PFU, respectively. As for symptoms, it is reported that the first observable sign of illness was fever. All six CMs in the high-dose group became ill. It is stated that three CMs had fevers and also that two CMs showed signs of encephalitis. Although it is not explicitly stated that the two CMs with encephalitis are a subset of the three with fever, a figure in the paper shows the recorded body temperatures for all six, and three CMs clearly had no fever and thus presumably did not become ill. Therefore, we assume that the two encephalitic CMs were indeed a subset of the three with fever. Table 226 explicitly states our interpretation of the Reed et al. data. Probit analysis of the Table 226 yields the following: $ID_{50} = 2\times10^6$ PFU (95% CI does not converge, indicating high uncertainty), and PS = 3.1 (95% CI 0.0–10.7). Although the uncertainty is obviously quite high, this estimate is the best one available, given the data.

[1032] Reed et al., "Aerosol Exposure to WEE Virus," 1178.

[1033] Ibid.

[1034] This interpretation is aided by the fact that these doses are reported to be "1 and 10 ID50," See Reed et al., "Aerosol Exposure to WEE Virus," 1178.

Table 226. NHP Data Used to Develop the WEEV Infectivity Model

Source	NHP Species	Challenge Route	Dose (PFU)	Number of NHPs Ill/ Challenged
Reed et al.	CM	Inhalation	2×10^6	3/6
	CM	Inhalation	2×10^7	6/6

Source: Reed et al., "Aerosol Exposure to WEE Virus."

Now it is important to consider how the CM estimate should be applied to humans. As discussed in Subsection 0, the estimated ID_{50} for VEEV is 10 PFU. However, the VEEV ID_{50} for CMs is 1.33×10^6 PFU,[1035] indicating that CMs are resistant to VEEV infection relative to humans. Given the similarity between VEEV and WEEV, it seems wise to assume that CMs are also more resistant to WEEV than humans. Thus, a scaling factor is needed. The only scaling factor available is that indicated by the ratio of the CM VEEV ID_{50} to the human VEEV ID_{50}s: 1.33×10^6 PFU/10 PFU = 1.33×10^5. Applying this ratio to the CM ID_{50} for WEEV: 2×10^6 PFU/1.33×10^5 = 15 PFU. Thus, 15 PFU is the ID_{50} used in *AMedP-7.5* for WEEV. The probit slope of 3.1 probits/log (dose) estimated from the CM WEEV data (see previous paragraph) is also used.

Lethality

As discussed in the introduction to this chapter, in naturally occurring cases, WEEV is less neuroinvasive than EEEV and less likely to lead to death in cases of neuroinvasion. Further, although some authors have argued that aerosol exposure is more likely to lead to neuroinvasion, the NHP data available are insufficient to make such a case. Thus, the model derived in this chapter ignores the incidence of WEE and focuses solely on WEEV disease. This decision is justified because *AMedP-7.5* is a planning tool, and such small percentages will have little effect on the overall planning. It is also consistent with other *AMedP-7.5* models.

Since WEEV infection only leads to death as a result of encephalitis (WEE) and the model derived in this chapter relates only to WEEV disease (a non-encephalitic syndrome), the CFR in *AMedP-7.5* is 0%.

Incubation Period

Before discussing the data used for the model, we must again consider the difference between WEEV disease and WEE: since WEEV disease occurs first chronologically, any data used for the incubation period model must clearly refer to the first onset of symptoms,

[1035] Pratt, Gibbs, Pitt, and Schmaljohn, "Use of Telemetry to Assess Vaccine-Induced Protection," 1058.

not the onset of encephalitis (particularly since encephalitis is actually excluded from the model).

Since the number of reports of NHP tests with WEEV are so few, a comparison cannot be made to determine whether the incubation period depends on the route of exposure. Although we have aerosol challenge data from Reed et al.,[1036] no dataset is available for another route of exposure with which the aerosol data can be compared. Given this uncertainty, one might prefer to use human data, even if the route of exposure is mosquito bite, because of species extrapolation uncertainty. However, despite many previously published epidemiological articles, no such data are available. This lack of data is not surprising, since few people will recall the exact day that they were bitten by a mosquito, and they may have been bitten by a mosquito on many days leading up to their illness.

We do have two data points for humans, both related to laboratory accidents. In the first case, infected chick embryo droplets were flung about the room by a centrifuge, covering a scientist with the liquid. Fourteen days later, he suddenly had a severe headache, nausea, and vomiting.[1037] The second laboratory case describes infected chick embryo splashing into the eye of a laboratory technician. His symptoms began 4 days after the accident.[1038]

The CDC does not have a webpage on the diseases caused by WEEV infection. *MABW* states that in humans, "the incubation period is 5 to 10 days for natural infection."[1039] This statement contrasts somewhat with the Reed et al. data for aerosol challenge of CMs,[1040] where the onset of symptoms occurred from 4 to 6 days later (see Table 227). This difference may relate to the species difference, or to the exposure route difference, or to both, or it may be entirely spurious since *MABW* does not cite a source, and the epidemiological reports that we have seen do not contain information that would allow estimation of an incubation period. The laboratory infection data span from the NHP data to longer durations than indicated by *MABW*, so they do not provide any clarity.

Given that the NHP data are the only traceable dataset (instead of single data point) available, we used them to derive an incubation period model. Table 227 summarizes the data. Reed et al. stated that the onset of fever occurred in 4 or 5 days,[1041] but we found the

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[1036] Reed et al., "Aerosol Exposure to WEE Virus."

[1037] Helwig, "Western Equine Encephalomyelitis Following Accidental Inoculation."

[1038] Gold and Hampil, "Equine Encephalomyelitis in a Laboratory Technician," 557.

[1039] Steele et al., "Alphavirus Encephalitides," 254.

[1040] Reed et al., "Aerosol Exposure to WEE Virus."

[1041] Ibid., 1174. Although the experiment included 12 macaques, only 9 had a fever.

figures to be slightly different, as reflected in the table. The data have arithmetic mean and standard deviation of 4.67 days and 0.87 days, respectively. The model is therefore a lognormal distribution[1042] with a mean of 4.7 days and a standard deviation of 0.9 days.

Table 227. WEE Incubation Period Data from Animal Studies

Source	Animal Model	WEEV Strain	Exposure Route	Incubation Period (Days)
Reed et al.	CM	CBA-87	Aerosol	4 (n = 5), 5 (n = 2), 6 (n = 2)[a]

[a] The report presented the data in a figure that was somewhat difficult to read. These values are our interpretation of the figure.

Source: Reed et al., "Aerosol Exposure to WEE Virus."

Injury Profile

Recall that the model includes WEEV disease, but not WEE. Case reports tend to not be helpful here because they focus on encephalitis. In describing the early phase of the disease, before the onset of encephalitis, *MABW* states, "symptoms usually begin with malaise, headache, and fever, followed by nausea and vomiting."[1043] Medscape states that "the prodromal phase is often short, averaging 1–4 days, and consists of fever, headache, chills, nausea, and vomiting." Of primary interest, Medscape also states that many patients "may never develop symptoms beyond that of the viral prodrome,"[1044] indicating that even if the disease does not progress to WEE, the symptoms are as described previously.

Table 228 shows the Injury Profile for WEEV disease: a single stage with flu-like symptoms, followed by recovery. If WEE had been included in the model, additional stages would be required. Injury Severity Level 2 (Moderate) was chosen because in most historical cases, people did not report to the hospital until the onset of encephalitis (so Injury Severity Level 3 would be inappropriate—see Table 2), and the symptoms definitely seem worse than Mild.

Table 228. WEEV Disease Injury Profile

	Stage 1
S/S	Fever; headache; nausea and vomiting; malaise and weakness
S/S Severity	2 (Moderate)

[1042] Lognormal distribution is assumed unless the data indicate otherwise, and, in this case, the data do not.

[1043] Steele et al., "Alphavirus Encephalitides," 254.

[1044] Mohan Nandalur, "Western Equine Encephalitis Clinical Presentation," last updated July 19, 2013, http://emedicine.medscape.com/article/233568-clinical.

Duration of Illness

MABW's comments related to the duration of illness relate only to cases of encephalitis, so they cannot be used to estimate the duration of WEEV disease. As noted in the previous section, Medscape states that "the prodromal phase is often short, averaging 1–4 days,"[1045] but the underlying data supporting this statement are not identified, and the references listed do not provide such information. For specific data, we first consider information available from laboratory infection case reports.

In the first reported laboratory case, by Fothergill, Holden, and Wyckoff, a newly hired laboratory worker began feeling ill on March 5th. On March 8th she was confined to her home "with what was at first thought to be influenza,"[1046] and on March 11th, she began exhibiting neurological symptoms. For the WEEV disease model, the data point from this report is 5 days, since the symptoms began on March 5th and the last day without neurological symptoms was March 10th. The route of exposure was not established in this case.

The second laboratory case report[1047] gives insufficient detail to determine the length of the WEEV disease portion of the illness. In the third laboratory case, reported by Gold and Hampil, a 29-year-old male worker was splashed in the face with infected egg liquid. The onset of encephalitis (symptoms including "stuporous and had to be roused to get ordinary answers") occurred 3 days after the onset of initial symptoms (headache).[1048]

We also found a number of reports that summarize clinical experience during a naturally occurring outbreak and provide some epidemiological information. Unfortunately, these reports do not provide much information that can be used for deriving a duration of illness model for WEEV disease. The information that these reports provide is found in the case histories they give, which tend to relate to the worst cases—those who died of encephalitis. The case histories also tend to be for children and the elderly. It is not clear whether the "prodrome" (WEEV disease) in these cases would be different than that for a case in a younger adult where encephalitis does not ensue. The following paragraphs summarize the usable information that we were able to extract from various sources. We estimated the duration of the "prodrome" (WEEV disease) based on the time elapsed between the onset of symptoms and admission to the hospital, unless specific symptom descriptions dictated otherwise.

[1045] Ibid.

[1046] Fothergill, Holden, and Wyckoff, "Western Equine Encephalitis in a Laboratory Worker," 206.

[1047] Helwig, "Western Equine Encephalomyelitis Following Accidental Inoculation," 291.

[1048] Gold and Hampil, "Equine Encephalomyelitis in a Laboratory Technician," 557.

Buss and Howitt reported[1049] on cases in Kern County, California, between 1938 and 1940, including four case histories. In all four cases, the approximate duration of the prodrome could not be determined from the description.

Rozdilsky, Robertson, and Chorney reported on eight fatal cases from a 1965 outbreak in Saskatchewan, Canada, giving case histories to the extent that they were known for each of the eight patients. For six patients, the case histories included a clear indication of the length of the "prodrome" or the WEEV disease stage, before the onset of encephalitis. The outbreak resulted in the hospitalization of 490 people, and "hundreds more were briefly indisposed but not hospitalized,"[1050] but data on these others have apparently not been published, except for the general statement that "most cases were mild and the patients recovered completely in a few days."[1051] This statement can be used as a consistency check for the final model.

Leech, Harris, and Johnson[1052] reported on 1975 outbreaks in North Dakota and Western Minnesota. In these outbreaks, 347 patients met the clinical criteria for possible infection and were examined, and 58 of the symptomatic were serologically confirmed to be infected with WEEV. Unfortunately, data were not reported for the 169 people who had "febrile headache" as their primary syndrome. Case histories are only given for three patients who died of encephalitis, and in only one of those cases can the approximate duration of the prodrome be identified.

More recently, Delfraro et al. reported on a single case involving a 14-year-old boy. From the description, it is clear that the viral prodrome was 5 days long.[1053] He eventually died from encephalitis. We examined a number of other reports on WEE outbreaks that did not contain any information that could be used for the duration of illness model. For brevity, they are not cited here. One report by Lennette and Longshore did not contain specific case information but, based on review of hundreds of cases, stated that "evidence

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1049 William C. Buss and Beatrice F. Howitt, "Human Equine Encephalomyelitis in Kern County, California, 1938, 1939, and 1940," *American Journal of Public Health* 31, no. 9 (1941): 935–944.

1050 B. Rozdilsky, H. E. Robertson, and J. Chorney, "Western Encephalitis: Report of Eight Fatal Cases: Saskatchewan Epidemic, 1965," *Canadian Medical Association Journal* 98, no. 2 (1968): 79.

1051 Ibid.

1052 Richard W. Leech, John C. Harris, and Robert M. Johnson, "1975 Encephalitis Epidemic in North Dakota and Western Minnesota. An Epidemiologic, Clinical, and Neuropathologic Study," *Minnesota Medicine* 64, no. 9 (1981): 545–548.

1053 Adriana Delfraro et al., "Fatal Human Case of Western Equine Encephalitis, Uruguay," *Emerging Infectious Diseases* 17, no. 5 (2011): 952–954.

of central nervous system involvement generally is not manifested until the third to fifth day following the onset of the illness."[1054]

Table 229 summarizes the total dataset we considered. A student's *t*-test comparisons indicated that there is no statistically significant difference between the human laboratory (first two sources) and human natural outbreak (last four sources) data ($p = 0.13$), although, admittedly, the sample size is rather small. A similar test showed that there was no significant difference in duration between survivors and non-survivors ($p = 0.44$). Thus, all the data were considered since the individual samples form a single population. The mean and standard deviation of all the Table 229 data are 4.4 days and 1.9 days, respectively (sample size = 14). We arbitrarily assigned a lognormal distribution for the purpose of modeling, consistent with most other submodels in *AMedP-7.5*.

Table 229. Duration of Illness in Human Cases of WEEV Disease

Source	Patient's Age	Apparent Duration of "Prodrome" (Days)	Outcome (Death or Survival)
Fothergill, Holden, and Wyckoff	30 years	3	Death
Gold and Hampil	29 years	2	Survival
Rozdilsky, Robertson, and Chorney	3 weeks	2	Death
	61 years	7	Death
	74 years	2	Death
	30 years	7	Death
	66 years	4	Death
	63 years	4	Death
Leech, Harris, and Johnson	81 years	3	Death
Buss and Howitt	5 months	7	Survival
	7 weeks	4	Death
	6 weeks	5	Survival
	30 years	6	Survival
Delfraro et al.	14 years	5	Death

Note: See Appendix B for full reference citations

This result is slightly longer than one would expect from the statements that most patients recovered in a "few" or 1 to 4 days. However, it is consistent with Lennette and Longshore's statement, based (loosely) on data from hundreds of patients, that CNS symptoms were generally not observed until the 3rd to 5th day of illness. Thus, although

[1054] Edwin H. Lennette and W. Allen Longshore, "Western Equine and St. Louis Encephalitis in Man, California, 1945-1950," *California Medicine* 75, no. 3 (1951): 193.

the model certainly carries uncertainty, particularly given that it is based on only 14 data points, it does seem consistent with the expectation that is most tied to actual data.

Medical Countermeasures and Treatment Model

The only available treatment for WEEV disease is palliative care.[1055] There are no vaccines or drugs available to prevent or treat WEEV disease (although there is ongoing research on vaccine development). Therefore, there are no WEEV disease treated submodels.

Model Summary

Table 230 and Table 231 summarize the model parameters for WEEV disease used in *AMedP-7.5*. Note that WEE, the disease involving the actual encephalitis for which the virus is named, is *excluded* from the model. While the parameters in these tables represent current best estimates, any new data that become available, particularly additional human data from natural cases, or that would enable comparison of NHP aerosol with NHP non-aerosol disease, would be helpful.

Table 230. WEEV Disease Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 15 PFU Probit slope = 3.1 probits/log (dose)
Lethality[a]	Rate	0%
Incubation period	Lognormal distribution	Mean = 4.7 days Standard deviation = 0.9 days μ = 1.530; σ = 0.190
Duration of illness	Lognormal distribution	Mean = 4.4 days Standard deviation = 1.9 days μ = 1.396; σ = 0.413

[a] The same rate is used for the "case encephalitis rate."

Table 231. WEEV Disease Injury Profile

	Stage 1
S/S	Fever; headache; nausea and vomiting; malaise and weakness
S/S Severity	2 (Moderate)

Cohorts and Special Considerations (*AMedP-7.5 Section 5.2.13.3*)

Cohort populations are calculated according to the standard equations for E, F, and S in *AMedP-7.5*; no further explanation is warranted.

[1055] Steele et al., "Alphavirus Encephalitides," 255.

1.30. Botulism Model
(*AMedP-7.5 Section 5.2.14*)

Introduction

Botulinum toxins are a set of neurotoxins, serotypes A through G, produced by the bacterium *Clostridia botulinum*. Exposure to the toxin via various pathways—ingestion, intramuscular injection, or inhalation—will cause the neuroparalytic disease botulism in humans. Botulism is most commonly caused by foodborne ingestion of toxin serotypes A, B, and E; other types of naturally occurring botulism include infant botulism and wound botulism. The disease is often fatal if untreated. Time to onset, severity of illness, and probability of death vary by serotype of toxin. Serotype A was selected as the basis for *AMedP-7.5* modeling of human response to botulism because serotype A is responsible for the plurality of human botulism cases reported in the United States and typically causes the most severe disease.[1056]

Human data on inhalation exposure are limited for botulism, although the few documented cases of inhalational botulism suggest that characteristics of the disease—with the exception of the gastrointestinal symptoms—are the same as that resulting from ingestion,[1057] for which significant information exists. Thus, given the available information, we assumed that the inhalation and ingestion forms of the disease are similar in course, signs and symptoms, and severity.

Assumptions, Limitation, and Constraints (*AMedP-7.5 Section 5.2.14.2*)

Assumption: All individuals weigh 70 kilograms.

This assumption is necessary because the toxicity data for the lethality model have been scaled to a weight of 70 kg.

Assumption: The inhalation and ingestion forms of botulism are similar in course, signs and symptoms, and severity, such that data from ingestion botulism may be used to inform models of inhalation botulism.

The introduction to this chapter provides sufficient explanation.

Limitation: Although the model requires the user to specify a day on which the antitoxin becomes available ($d_{trt\text{-}bot}$), it does *not* apply the antitoxin to

[1056] Bradley A. Woodruff et al., "Clinical and Laboratory Comparison of Botulism from Toxin Types A, B, and E in the United States, 1975–1988," *The Journal of Infectious Diseases* 166, no. 6 (December 1992): 1281.
[1057] E. Holzer, "Botulism Caused by Inhalation," Medizinische Klinik, 41 (1962) 1735–1740 (German language version), 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 (2007): 122–134.

every person on that day; only those who have been declared WIA are modeled to receive antitoxin on that day. Those who are declared WIA after $d_{trt\text{-}bot}$ are modeled to receive the antitoxin on the day they are declared WIA.

Although this is stated as a limitation, it is actually the most sensible way to apply treatment.

Constraint: The models are based on Serotype A.

This was a model developer choice; the introduction to this chapter provides sufficient explanation of why.

Constraint: Upon receiving antitoxin, individuals are modeled to complete the stage they are already in without modification of that stage's duration of illness due to receiving the antitoxin. The duration(s) of subsequent stage(s) of illness are modified because of the antitoxin.

In reality, as soon as patients receive the antitoxin they will start improving, so the stage of disease they are in when they receive the antitoxin will be shortened. However, the nature of the duration of illness model for botulism is such that this cannot be implemented without a great increase in complexity of the model. The increased complexity would not be worth the modest gains in accuracy.

Human Response Model (*AMedP-7.5 Tables 5-104 to 5-106*)

Effectivity

We conducted a literature search to locate botulism effectivity data from human intoxication cases or animal studies. However, no published data were available for use in determining the effective dose of botulinum toxin, so we sought advice during the NATO Subject Matter Expert Meeting in May 2008 (Madrid, Spain) as part of the development of *AMedP-8*(*C*). Based on their experience with animal studies with botulism for vaccine development, the SMEs suggested using an ED_{50} of 0.1 μg/man.

In the absence of published data to calculate an effective dose-response curve, the effectivity submodel probit slope was assumed to be equivalent to the probit slope derived for the lethality submodel (see the next subsection). This assumption was used, and later approved by SMEs, because steep dose-response curves have been observed in animal studies for both effectivity and lethality. The assumed probit slope is 12.5 probits/log (dose).

Lethality

The botulinum neurotoxin serotype A inhalation LD_{50} for RMs has been demonstrated to be 300–400 mouse intraperitoneal median lethal doses ($MIPLD_{50}$) per kilogram of body

weight.[1058] Crystalline toxin assays indicate between 2.8×10^{10} and 3.2×10^{10} $MIPLD_{50}$ per gram of botulinum toxin.[1059] Assuming a 70 kg man, an average RM inhalation LD_{50} dose of 350 $MIPLD_{50}$/kg, and an average assay of 3.0×10^{10} $MIPLD_{50}$/g gives a human LD50 of 0.8 μg/man. This is consistent with the human inhalation LD_{50} of 0.7 to 0.9 μg estimated in Dembek et al.;[1060] note, however, that the estimate is essentially for a 70 kg RM—no uncertainty factor was used to convert from the NHP model to humans.

We were unable to find inhalation NHP data that could be used to derive a probit slope. Instead, we used dose-response data for intravenous administration of botulinum toxin in RMs from Herrero et al.[1061] The Herrero data—provided for doses ranging from slightly below the calculated monkey LD_{50} to those where all monkeys died—are shown in Table 232. Admittedly, the lack of data at lower doses means this probit slope estimate could be improved with additional data. There are also the obvious problems of extrapolating from intravenous to inhalation and from NHPs to human, but these could not be avoided given the data available.

Probit analysis on the Table 232 data yields a probit slope of 12.5 probits/log (dose), which is the value used for the effectivity and lethality models for botulism.

[1058] David R. Franz et al., "Efficacy of Prophylactic and Therapeutic Administration of Antitoxin for Inhalation Botulism," in *Botulinum and Tetanus Neurotoxins: Neurotransmission and Biomedical Aspects*, ed. Bibhuti R. Dasgupta (New York, NY: Plenum Press, 1993), 473.

[1059] William C. Patrick III, "Analysis of Botulinum Toxin, Type A, as a Biological Warfare Threat," May 1998.

[1060] Zygmunt F. Dembek, Leonard A. Smith, and Janice M. Rusnak, "Botulinum Toxin," chap. 16 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), 340.

[1061] Brunildo A. Herrero et al., "Experimental Botulism in Monkeys—A Clinical Pathological Study," *Experimental and Molecular Pathology* 6, no. 1 (February 1967): 84–95.

Table 232. RM Intravenous Botulinum Toxin Lethality Data

Dose ($MIPLD_{50}$/kg)	# RMs Challenged	# RMs Dead
37.8	6	3
44.0	6	2
46.0	6	5
52.0	6	5
55.0	6	6
55.0	6	6
65.0	6	6

Latent Period

A review by Woodruff et al. of botulism cases in the United States from 1975 to 1988 concluded that there were 148 cases of type A botulism in this time period. Information on the latent period duration existed for approximately 110 of these—76 illnesses associated with outbreaks and 34 illnesses associated with sporadic cases. Of these, 42 cases associated with outbreaks and 24 cases associated with sporadic intoxications had latent periods of less than or equal to 1 day. From this, the study's authors concluded that "the median [latent] period for all patients was 1 day (ranges: 0–7 days, type A; 0–5 days, type B; 0–2 days, type E)."[1062] Although reputable sources such as *MMBC*[1063] indicate that the latent period is dose-dependent, the challenge dose in human cases is unknown, so it was not possible to create a dose-dependent model.

Assuming that the median latent period of 1 day described for all types of botulism is also the median time for Type A botulism and that the latent periods were lognormally distributed, we performed a fit analysis to estimate the parameters associated with a lognormal distribution with a median of 1 day and a range of 0–7 days. Such an approach is suggested by Walden and Kaplan for incubation periods described only by a range of times.[1064] Since the median value of a lognormal distribution is defined as e^{μ}, where the parameter μ is the mean of the natural logarithm of the observed random variables (in this case, the latent periods), μ is easily calculated to be 0. To account for the range of incubation period values, the second parameter of the lognormal distribution, σ, was manipulated until the CDF evaluated at 7 days was equal to 0.99, which was the case when $\sigma = 0.84$. With the values $\mu = 0$ and $\sigma = 0.84$, one can calculate a mean and standard deviation of 1.42 and 1.44 days, respectively.

[1062] Woodruff et al., "Clinical and Laboratory Comparison," 1282.

[1063] USAMRIID, *Medical Management of Biological Casualties*, 123–124.

[1064] John Walden and Edward H. Kaplan, "Estimating Time and Size of Bioterror Attack," *Emerging Infectious Diseases* 10, no. 7 (July 2004): 1202.

Injury Profile

Symptom descriptions were compiled from Arnon et al.,[1065] Dembek et al.,[1066] and Hughes et al.[1067] Based on these references, we split the Injury Profile into three stages, with Stage 3 being different for survivors and non-survivors.

Table 233. Botulism Injury Profile

	Stage 1	Stage 2	Stage 3 (non-survivors)	Stage 3 (survivors)
Signs and symptoms (S/S)	Fatigue; dry mouth; ptosis; diplopia; photophobia; dysphagia; dysarthria; dysphonia; facial paralysis	Acute symmetrical descending flaccid paralysis: progressive muscle weakness in the head and neck, followed by upper extremities and lower extremities; dysphagia and loss of gag reflex; diplopia; dysarthria; dysphonia; fatigue	Acute symmetrical descending flaccid paralysis: paralysis in respiratory muscles and upper and lower extremities; respiratory failure	Gradual reversal of muscle paralysis
S/S Severity	2 (Moderate)	3 (Severe)	4 (Very Severe)	2 (Moderate)

Duration of Illness

Although human data exist from botulism outbreaks, all recorded cases had received some form of treatment, which could alter human response—these cases can only be used for the treated model.

However, we found time-to-death data for RMs challenged intravenously with varying levels of botulinum toxin serotype A, described in detail in Herrero et al.[1068] and Oberst et al.[1069] The two datasets were combined, and the resulting 41 data points are shown in Table 234. Animals number 29, 32, and 45 from the Oberst study were excluded because the time-of-onset data were inadequate. To be consistent with the precision of the Herrero figures, the Oberst length of illness data were rounded to the nearest day before any analysis

[1065] Stephen S. Arnon et al., "Botulinum Toxin as a Biological Weapon: Medical and Public Health Management," *Journal of the American Medical Association* 285, no. 8 (February 2001): 1059–1070.

[1066] Dembek, Smith, and Rusnak. "Botulinum Toxin."

[1067] James M. Hughes et al., "Clinical Features of Types A and B Food-borne Botulism," *Annals of Internal Medicine* 95, no. 4 (October 1981): 442–45.

[1068] Herrero et al., "Experimental Botulism in Monkeys."

[1069] Fred W. Oberst et al., *Botulinum Antitoxin as a Therapeutic Agent in Monkeys with Experimental Botulism*, CRDLR 3331 (Edgewood, MD: U.S. Army Edgewood Arsenal Chemical Research and Development Laboratories, October 1965), AD627996.

was performed. Although some sources, such as *MABW*,[1070] indicate that the duration of illness may be dose-dependent, the Herrero and Oberst data do not suggest dose-dependence, so we created a dose-independent model based on the Table 234 data.

Fitting of the Table 234 data using the @RISK software[1071] yields an exponential distribution with $\lambda = 0.318$ (mean total duration of 3.14 days). Lacking other information to enable a data-driven splitting of the total non-survivor duration into smaller durations for each stage, we simply assumed each stage had equal duration. Thus each stage is modeled with an exponential distribution with $\lambda = 0.954$, or a mean duration of 1.04 days.

Table 234. Botulism Non-Survivor Time to Death Data (from Intravenously Challenged RMs)

Source	Animal Number	Day of Onset[a]	Day of Death[a]	Duration of Illness
Herrero	2	2	5	3
	7	2	5	3
	9	1	4	3
	10	1	4	3
	11	1	3	2
	12	1	4	3
	14	1	6	5
	16	1	3	2
	17	1	3	2
	18	1	3	2
	19	2	4	2
	20	1	5	4
	23	1	6	5
	24	1	5	4
	25	1	6	5
	26	1	2	1
	28	2	7	5
	30	1	5	4
	31	1	5	4
	32	1	5	4
	33	1	3	2
	37	2	8	6
	38	2	6	4

[1070] Dembek, Smith, and Rusnak. “Botulinum Toxin,” 340.
[1071] *@Risk for Excel*.

Source	Animal Number	Day of Onset[a]	Day of Death[a]	Duration of Illness
	39	2	7	5
	40	2	5	3
	41	1	7	6
	42	2	5	3
	56	1	11	10
	59	2	5	3
	60	1	8	7
Oberst	17	1.21	1.58	0.38
	19	1	1.33	0.33
	20	0.85	1.58	0.74
	23	1.42	2.04	0.63
	33	1.64	2.04	0.4
	35	1.58	5.42	3.83
	40	1.71	2.79	1.08
	41	1.59	2.79	1.2
	51	1.17	2.67	1.5
	60	1.19	2.04	0.85
	64	1.43	3.04	1.61

[a] "Day" means day post-exposure

We found no data for the duration of illness in untreated survivors. Thus, we had to make assumptions: we assumed that survivors would not begin to recover for several weeks and that full recovery would take several months (Stage 1 duration of 1 day, Stage 2 duration of 14 days, and Stage 3 duration of 180 days). These values are based loosely the *MABW* statement that "mechanical ventilation may be required for 2 to 8 weeks with foodborne botulism, with paralysis lasting as long as 7 months."[1072] Naturally, given the lack of data, the models are constant periods instead of probability distributions.

Medical Countermeasures and Treatment Model

Medical management of botulism patients has two primary objectives: to arrest progression of the disease through the body as quickly as possible and to maintain life through supportive care until the patient recovers. Supportive care would initially focus on maintenance of ventilation, but would also include infection control and physical therapy during recovery.

[1072] Dembek, Smith, and Rusnak. "Botulinum Toxin," 341.

At present there are no FDA-approved vaccines for the prevention of botulism. A formalin inactivated pentavalent toxoid vaccine, which protected against botulinum toxin serotypes A through E, was administered to laboratory personnel and other at-risk individuals from 1959 through 2011; the CDC recently stopped providing this vaccine, due to declining immunogenicity—possibly due to the age of the drug—and increased occurrence of moderate local reactions.[1073]

Botulinum antitoxin—both despeciated equine antitoxin and human botulism immune globulin—can effectively prevent botulism if administered immediately before or shortly after exposure.[1074] However, antitoxin has limited availability, requires refrigeration, offers short-lived protection, and carries significant risk of anaphylaxis. It is therefore not generally recommended for use in asymptomatic individuals. In those with known exposure to botulinum toxin, the risks from administration of antitoxin must be weighed against the risk of disease.[1075] The American Medical Association (AMA) recommends that asymptomatic individuals who are believed to have been exposed should remain under close medical observation and, if feasible, near critical care services.[1076] In 2013, the FDA approved[1077] a heptavalent antitoxin.

Although antitoxin will effectively prevent further paralysis within hours of its administration, the progression of paralysis in botulism patients is so rapid that antitoxin cannot typically be administered quickly enough to avoid respiratory paralysis. Thus, most botulism patients will require assisted ventilation: in a study of all reported botulism patients in the United States from 1975 through 1988, 60% of those with serotype A botulism required intubation and assisted ventilation, and the average time from onset to intubation was 1 day.[1078]

While antitoxin can prevent the further progression of paralysis, it does not reverse it. Recovery from botulism is slow, with mechanical ventilation required for several weeks and paralysis persisting for months.[1079]

[1073] Dembek, Smith, and Rusnak. “Botulinum Toxin,” 345.

[1074] Franz et al., “Efficacy of Prophylactic and Therapeutic Antitoxin.”

[1075] Dembek, Smith, and Rusnak. “Botulinum Toxin,” 344.

[1076] Arnon et al., “Botulinum Toxin as a Biological Weapon,” 1068.

[1077] U.S. Food and Drug Administration, “FDA approved first Botulism Antitoxin for use in neutralizing all seven known botulinum nerve toxin serotypes,” last modified March 22, 2013, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm345128.htm.

[1078] Woodruff et al., “Clinical and Laboratory Comparison,” 1283.

[1079] Dembek, Smith, and Rusnak. “Botulinum Toxin,” 343–344.

Pre-Exposure Prophylaxis

Experience with the pentavalent toxoid vaccine suggests that countermeasures could be very effective in preventing the disease. For example, from 1945 to 1969, 50 accidental exposures to botulinum toxins occurred at Fort Detrick among vaccinated laboratory workers, but none developed botulism.[1080] Tests with early formulations of recombinant vaccines against serotypes A and B demonstrated that when vaccinated three times, mice were fully protected against intraperitoneal challenge doses of 10^5 mouse LD_{50}.[1081]

Although, at present, there are no FDA-licensed vaccines against botulism available, should vaccinated individuals be included in a population at risk for purposes of casualty estimation, they should be considered fully protected against the development of botulism.

Lethality

The overall case fatality rate for treated cases of naturally occurring type A botulism in the United States is 7%. Death was the result of respiratory failure or secondary infection resulting from prolonged mechanical ventilation.[1082] Since overall some 60% of type A botulism patients required mechanical ventilation, the fatality rate for ventilated patients was 12%.

For the *AMedP-7.5* models, those individuals that are estimated to survive according to the untreated (dose-dependent) lethality model become part of the "survivors, treated, sublethal dose" cohort. Those who received a lethal dose are split among several further sub-cohorts, depending in part on the time at which they receive antitoxin. All lethal dose individuals who receive antitoxin before entering Stage 3 of the disease are assumed to survive, and they become part of a "treated, unventilated" survivor cohort, with "unventilated" meaning that respiratory support is not required to ensure their survival. Lethal dose individuals who receive antitoxin while in Stage 3 have two possible outcomes: 12% are estimated to die despite medical treatment and become part of the "non-survivors, treated ventilated" cohort, and the remaining 88% become part of the "survivors, treated ventilated" cohort.

Injury Profile and Duration of Illness

In one case study comparing the clinical features of type A and type B botulism, Type A patients requiring mechanical ventilation were ventilated for a mean duration of 58 days,

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[1080] Dembek, Smith, and Rusnak, "Botulinum Toxin," 345.

[1081] Michael P. Byrne and Leonard A. Smith, "Development of Vaccines for the Prevention of Botulism," *Biochimie* 83, no. 9–10 (2000): 962.

[1082] Hughes et al., "Clinical Features of Types A and B Food-Borne Botulism," 444.

and were hospitalized for a mean of 63 days.[1083] In this study, no information was provided regarding duration of hospitalization for cases where ventilation was not required.

Another case study specifically assessed the course of clinical recovery from Type A botulism in the second largest outbreak of the disease recorded in the United States, which involved 34 people who ingested toxin at a restaurant in Clovis, New Mexico, in April 1978.[1084] All patients in this outbreak were hospitalized, all but one received antitoxin, and two died. The authors of the study interviewed 27 survivors at either 9 or 13 months after the outbreak and provided them with a written questionnaire 24 months afterward. This study found that those who required mechanical ventilation had a mean duration of hospitalization of 76.4 days, with a range of 19 to 164 days. Those who did not require ventilation had a mean duration of hospitalization of 7.3 days, with a range of 4 to 17 days.[1085]

The study also found that symptoms persisted for longer periods of time and in greater numbers among patients requiring ventilation. At 24 months, those cases reported a mean of five persistent symptoms, while the unventilated cases reported a mean of two persistent symptoms. Data on return to work showed that virtually all the unventilated patients had resumed a full work schedule within 9 months of the outbreak, while only 25% of ventilated patients had done so.[1086]

The durations of illness stated in the following paragraphs are based on data from the Clovis outbreak and on the untreated duration of illness model.

Because CONV casualties can be included in estimates that account for medical treatment, sublethal dose survivors progress through a shortened Stage 2 (7 days) and then enter CONV instead of progressing to Stage 3; the duration of their convalescence is the same as Stage 3 for untreated survivors (180 days).

Individuals who receive a lethal dose but also receive antitoxin in Stage 1 complete the untreated Stage 1 duration of illness before a 7-day Stage 2 and then a 270-day CONV. Individuals who receive a lethal dose but also receive antitoxin in Stage 2 complete the untreated Stages 1 and 2 duration of illness before a 270-day CONV.

Since ventilated non-survivors and survivors do not receive antitoxin until after the onset of Stage 3, they progress through the first two stages of illness according to the untreated model. They then have a 70-day Stage 3 (while on a ventilator). At the end of the

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[1083] Ibid., 444.

[1084] J. M. Mann et al., "Patient Recovery from Type a Botulism: Morbidity Assessment Following a Large Outbreak," *American Journal of Public Health* 71, no. 3 (1981).

[1085] Ibid., 266.

[1086] Ibid., 268.

time spent on a ventilator, non-survivors die and survivors enter indefinite CONV—it is assumed that they will either never RTD or the time to RTD is so long that it is practically "never" for the purpose of planning an operation.

Model Summary

Table 235 and Table 236 summarize the model parameters for botulism used in *AMedP-7.5*. The model was derived from human data (likely ingestion) and NHP data (intravenous). If inhalation data or additional human data become available, the models could likely be improved. In particular, *any* relevant effectivity data would improve the model, since it is currently based on an SME estimate.

Table 235. Botulism Model Parameters Summary Table

Submodel	Type	Parameters
Effectivity	Lognormal distribution	ID_{50} = 0.1 µg/man Probit slope = 12.5 probits/log (dose)
• Pre-exposure vaccination	Rate (efficacy)	100%
Lethality	Lognormal distribution	ID_{50} = 0.8 µg/man Probit slope = 12.5 probits/log (dose)
Latent period	Lognormal distribution	Mean = 1.42 days Standard deviation = 1.44 days μ = 0; σ = 0.84
Duration of illness		
• Stages 1, 2, and 3, each (non-survivors, anyone who has not *yet* received antitoxin)	Exponential distribution	Mean = 1.04 days λ = 0.954
• Stage 1 (untreated survivors and sublethal dose treated survivors)	Constant	1 days
• Stage 2 (untreated survivors)	Constant	14 days
• Stage 3 (untreated survivors)	Constant	180 days
• Stage 2 (sublethal dose treated survivors, Stage 1 treated unventilated survivors)	Constant	7 days
• CONV (sublethal dose treated survivors)	Constant	180 days
• CONV (all treated unventilated survivors)	Constant	270 days
• Stage 3 (treated ventilated survivors and non-survivors)	Constant	70 days
• CONV (treated ventilated survivors)	Constant	Indefinite

Table 236. Botulism Injury Profile

	Stage 1	Stage 2	Stage 3 (non-survivors)	Stage 3 (survivors)
Signs and symptoms (S/S)	Fatigue; dry mouth; ptosis; diplopia; photophobia; dysphagia; dysarthria; dysphonia; facial paralysis	Acute symmetrical descending flaccid paralysis: progressive muscle weakness in the head and neck, followed by upper extremities and lower extremities; dysphagia and loss of gag reflex; diplopia; dysarthria; dysphonia; fatigue	Acute symmetrical descending flaccid paralysis: paralysis in respiratory muscles and upper and lower extremities; respiratory failure	Gradual reversal of muscle paralysis
S/S Severity	2 (Moderate)	3 (Severe)	4 (Very Severe)	2 (Moderate)

Cohorts and Special Considerations (*AMedP-7.5 Section 5.2.14.3*)

Given the discussion above about the importance of administering the antitoxin before the onset of Stage 3, the equations below are obviously highly dependent on the user's choice for the value of $d_{trt\text{-}bot}$. The user's choice is reflected in the parameters P_{DOW}, $P_{in\text{-}Stg3}$, and $P_{in\text{-}Stg2}$, which are looked up in *AMedP-7.5* Tables 5-101 to 5-103; once the values of these parameters is determined, the equations to calculate the cohort populations are straightforward: they involve the application of a probability of being at a certain point in the progression of illness to a certain population, by simply multiplying. The "hard-coded" factors 0.12 and 0.88 in *AMedP-7.5* Equations 5-75 and 5-76 reflect the expectation that 12% of those who require mechanical ventilation will die. The only other concept used in the equations is the mutual exclusivity of the cohorts, which leads to the subtraction of certain cohort populations in some of the equations.

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1.31. Ricin Intoxication Model (*AMedP-7.5 Section 5.2.13*)

Introduction

Ricin is a protoplasmic poison derived from waste that is left over from processing seeds of the castor bean plant known as *Ricinis communis*. The castor bean is composed of 35% to 55% of fast-drying, non-yellowing oil (castor oil) that was historically used as a lubricant for machinery, inks, varnishes, and dyes.[1087] The waste mash from castor oil production is 3%–5% ricin by weight.[1088] Ricin is a protein in the type II family of ribosome-inactivating proteins (RIPs). The toxin is made of two polypeptide chains. The B chain binds to cell surface receptors, and the toxin-receptor complex enters the cell. The A chain endonuclease activity inhibits protein synthesis. After enough protein synthesis has been inhibited, symptoms of ricin toxicity begin to appear.[1089]

Although ricin is highly toxic, it is significantly less toxic than botulinum toxin or tetanus. However, while the last two agents are relatively difficult to acquire, purified ricin continues to be widely available due to its utility in the biotechnology and pharmaceutical industries. Purified ricin is stable under typical ambient conditions but is relatively easy to detoxify using acids, alkalis, halogens, or grinding and pulverizing.[1090]

Ricin does not reaerosolize significantly[1091] or spread from person to person through casual contact. Moreover, ricin poisoning also cannot spread from person to person through contact with body fluids.[1092] We modeled ricin as a noncontagious biological agent.

Ricin is toxic via multiple routes of exposure. Animal models have shown that the progression of symptoms is very dependent on the route of exposure,[1093] so inhalation data were preferred for deriving submodel parameters. Naturally occurring cases of ricin

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[1087] Mark A. Poli et al., "Ricin," chap. 15 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), 324.

[1088] USAMRIID, *Medical Management of Biological Casualties*, 130.

[1089] Poli et al., "Ricin," 325.

[1090] Harry L. Craig et al., Preparation of toxic ricin, U.S. Patent 3060165, filed 3 July 1952, and issued 23 October 1962.

[1091] USAMRIID, *Medical Management of Biological Casualties*, 129.

[1092] G. A. Balint, "Ricin: The Toxic Protein of Castor Oil Seeds," *Toxicology* 2, no. 1 (1974): 78.

[1093] Gareth D. Griffiths et al., "Inhalation Toxicology and Histopathology of Ricin and Abrin Toxins," *Inhalation Toxicology* 7, no. 2 (1995): 269–288; Catherine L. Wilhelmsen and M. L. M. Pitt, "Lesions of Acute Inhaled Lethal Ricin Intoxication in Rhesus Monkeys," *Veterinary Pathology* 33 (1996): 296–302; Chad J. Roy et al., "Animal Models of Ricin Toxicosis," *Current Topics in Microbiology and Immunology* 357 (2012): 243–257.

poisoning in humans are generally due to ingestion of castor beans, so they were not useful for developing the model.

Assumptions (*AMedP-7.5 Section 5.2.15.2*)

Assumption: All individuals weigh 70 kilograms.

This assumption is necessary because the toxicity data for the lethality model have been scaled to a weight of 70 kg.

Assumption: The effectivity probit slope is equal to the lethality probit slope.

See Subsection 0.

Human Response Model (*AMedP-7.5 Tables 5-121 and 5-122*)

Importance of Plant Type and Method of Preparation

The castor oil plant has at least 21 varieties, and each contains ricin.[1094] The only available study that directly compares the toxicity of ricin from different types of castor oil plant concludes that the "Hale Queen" variety is almost threefold more toxic than *R. zanzibariensis*.[1095] The authors state that both samples were determined to be "pure" based on a specific laboratory technique, but no quantitative assessment of the purity was provided. If the samples were not of equivalent purity, the results could be significantly affected. Research in the 1960s showed that the toxicity can vary by at least an order of magnitude just by improving the preparation method to achieve more pure ricin.[1096] It is also possible that the particular impurities that remain in each source of ricin, which are a function of the plant variety from which they were derived, are the primary factor in determining differences in lethality. After all, there is only one "ricin." Thus, we believe the plant variety is not very important, but the preparation method is likely very important.

Ideally, the submodel parameters would account for this dependence, but the reality is that the data are insufficient. This lack of specificity in the model could result in *AMedP-7.5* producing an underestimate or overestimate of the number of casualties, depending on the specific ricin used in an attack.

Literature Summary

We reviewed over 80 publications, mostly peer-reviewed journal articles and government-sponsored studies, during the development of the ricin submodels.

[1094] Balint, "Ricin: The Toxic Protein," 77.

[1095] Griffiths et al., "Inhalation Toxicology and Histopathology of Ricin," 269.

[1096] Masatsune Ishiguro et al., "Biochemical Studies on Ricin 1. Purification of Ricin," *Journal of Biochemistry* 55, no. 6 (1964): 587–592.

Human Data

MABW and *MMBC* were useful for a general understanding of ricin intoxication, but we discovered only one documented case of human inhalational exposure to ricin. *MMBC* states, "Accidental sublethal aerosol exposures, which occurred in humans in the 1940s, were characterized by onset of fever, chest tightness, cough, dyspnea, nausea, and arthralgias within 4 to 8 h."[1097] In attempting to find further detail on these exposures, we found that a similar statement appears in the first edition of *MMBC*, but no further information or reference to a more detailed report is provided. We were unable to locate such a report and assume that it does not exist. Presumably, these exposures occurred during tests related to the U.S. offensive biological weapons program, which was studying ricin and even created and tested a ricin bomb,[1098] but no other information on these exposures is available.

Thus, by necessity, the data used to derive the submodel parameters come almost entirely from laboratory experiments with animals, the reports of which often do not include all the details one might desire related to the exact dose and timing of symptoms. The end result is that human response to an aerosol challenge of ricin is difficult to model, even after making the assumption that data from animal models are applicable.

Animal Data

NHPs are generally preferred as sources of data over other animals. This is particularly true with ricin because (1) aerosolized ricin produces injuries concentrated in the lungs,[1099] and (2) the geometry of the NHP lung is more similar to the human lung than is the geometry of other species' lungs.

The body of literature describing ricin inhalation experiments with animal models is a somewhat limited. Although non-inhalation animal experiments have been reported,[1100] we chose not to use these experiments. Most of the reports that we found were focused on deriving an LD_{50} estimate. We found very little usable data on the effectivity, latent period, or duration of illness other than time to death, so we have low confidence in those estimates. Finally, since we were unable to acquire some of the original reports, we relied on descriptions of the reports published elsewhere (these cases are noted in footnotes).

[1097] USAMRIID, *Medical Management of Biological Casualties*, 131.

[1098] Poli et al., "Ricin," 325.

[1099] Griffiths et al., "Inhalation Toxicology and Histopathology of Ricin"; Wilhelmsen and Pitt, "Lesions of Acute Inhaled Lethal Ricin."

[1100] For example, Ø. Fodstad et al., "Toxicity of Abrin and Ricin in Mice and Dogs," *Journal of Toxicology and Environmental Health* 5, no. 6 (1979): 1073–1084; Ø. Fodstad, S. Olsnes, and A. Pihl, "Toxicity, Distribution and Elimination of the Cancerostatic Lectins Abrin and Ricin after Parenteral Injection into Mice," *British Journal of Cancer* 34, no. 4 (1976): 418–425.

Finally, we are aware of ongoing research into the development of a ricin vaccine, which includes NHP testing and control animals. We contacted Soligenix with a request for data from experiments with control animals but did not receive a response in time to incorporate the data into the models. If such data become available, they could be used to revise the models for the next version of *AMedP-7.5*.

Lethality

Because there are no quantitative data on the inhalation toxicity of ricin to humans, animal models must provide the data for generating the submodel parameters. On a dose-per-mass basis, the LD_{50} varies over two orders of magnitude between species of domestic and laboratory animals.[1101] The decision of which animal model or models to use will have a significant impact on the accuracy of the LD_{50}. The decision may be less crucial for the PS.

The literature seems to focus on rodents, and one source even states that the "toxicity of ricin in man has been assumed to be roughly comparable to that for the mouse,"[1102] but there does not appear to be published analysis to support this assumption. Presumably, the real reason for the focus on rodents is that experiments with rodents are inexpensive and easy relative to experiments with larger animals, such as NHPs. Given that the physics of particle deposition and the subsequent health effects are highly dependent on the geometry of the respiratory system, it seems odd to assume that rodents are good models of humans. We did not use rodent data because we found sufficient NHP data to estimate an LD_{50} and PS.

We found two reports that provide an LD_{50} estimate based on NHP data: one from RMs and one from AGMs. We were unable to acquire the first report, which was published in 1995. Several other authors state that Pitt reported an LD_{50} of 15.0 µg/kg, based on RM data; however, more recently, Griffiths stated that the value should have been 5.0 µg/kg,[1103] citing personal communication with a colleague of Pitt.[1104] In 2012, Roy et al.[1105] reported some individual dose-response data from AGMs and RMs. In reporting the RM data, they appeared to reference the earlier work by Pitt. Table 237 summarizes the usable data

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[1101] Balint, "Ricin," Table III, summarizes the supporting data. Balint cites Miessner and Rewald, *Z. Immunitätsforsch*. 2 (1909) 323–349, as the data source. We were unable to acquire the Miessner and Rewald report.

[1102] Don T. Parker, Andrew C. Parker, and C. K. Ramachandran, *Joint CB Technical Data Source Book*, vol. VI, *Toxin Agents*, pt. 3*:* "Ricin" (Dugway Proving Ground: Joint Contact Point Directorate, February 1996), 18.

[1103] A more specific explanation of why a different value was originally reported is not offered.

[1104] Gareth D. Griffiths, "Understanding Ricin from a Defensive Viewpoint," *Toxins* 3, no. 11 (2011): 1378.

[1105] Roy et al., "Animal Models of Ricin Toxicosis."

reported by Roy et al. Two additional RM data points were not usable because it is stated that after the RMs had survived 48 hours, they were sacrificed, so it is not clear if those RMs would have survived or died. For the AGM data, Roy et al. make clear that the particle size was in the appropriate range (mass median aerodynamic diameter was 1 μm).

Table 237. Data from Roy et al. Used in Probit Analysis

Inhaled Dose (μg/kg)	NHP Tested	NHP Outcome
4.4	1 AGM	Died
1.9	1 AGM	Survived
5.2	1 AGM	Survived
3.4	1 AGM	Survived
13.7	1 AGM	Died
11.3	1 AGM	Died
4.5	1 AGM	Survived
4.8	1 AGM	Died
36.5	1 RM	Died
41.8	1 RM	Died
36.6	1 RM	Died

Based on the AGM data, Roy et al. report an LD_{50} estimate of 5.8 μg/kg, but they did not report a 95% CI. Based on the same data, we used probit analysis to estimate an LD_{50} of 4.9 μg/kg (the 95% CI calculation failed because of an attempt to take the square root of a negative number, which indicates a "very wide" CI) and a PS estimate of 6.1 probits/log (dose) with a 95% CI of 0 to 22. Clearly, the small number of data points is resulting in very large uncertainty. However, it is worth noting that ricin, as a toxin, should be expected to have a PS that is high relative to infectious biological agents and closer to values for chemical agents, which is indeed the case. Chemical agent PSs for *AMedP-7.5* range from about 6 (inhaled HD, percutaneous VX) to over 10 (most inhaled agents).

Although the uncertainty is large, these data are the only NHP data available. We contacted Soligenix with a data request but did not receive a response in time to include any additional data in the derivation.

Scaling 4.9 μg/kg to a 70 kg human, the estimate is 343 μg; the lethality model for ricin is a lognormal distribution with a PS of 6.1 probits/log (dose) and an LD_{50} of 343 μg.

Effectivity

We did not find any human data that could be used to develop an effectivity model. In addition, none of the animal data we found provided a clear path to an effectivity model.

Although Griffiths et al. stated that some of the rats they dosed showed no outward symptoms,[1106] they did not attach that comment to a specific dose. The lowest dose they reported, 1.05 µg/kg,[1107] is 29% of the LD_{50} we calculated from their data (calculation not presented), so an estimated lower bound on the ED_{50} for rats is 29% of the LD_{50}.

In a recent study, Bhaskaran et al.[1108] exposed RMs to aerosolized ricin. Of the three macaques that received nonlethal doses, all experienced symptoms, and the lowest dose was 1.9 µg/kg. Although there is uncertainty given only three data points, 1.9 µg/kg is one estimate of an upper bound on the ED_{50}. Based on the LD_{50} estimate in the previous section, 1.9 µg/kg is 39% of the LD_{50}.

Although the data are admittedly not ideal, if we assume that the ratio of ED_{50}/LD_{50} for RMs and mice are bounding cases for humans, then the ED_{50} is between 29% and 39% of the LD_{50}. We arbitrarily chose 35%. Thus, the ED_{50} for the model is 0.35×4.9 µg/kg = 1.72 µg/kg, or 120 µg for a 70 kg human.

Since no other information is available, we assumed that the PS from the lethality model could be applied to effectivity. Thus, the effectivity model is a lognormal distribution with a PS of 6.1 probits/log (dose) and an ED_{50} of 120 µg. This effectivity model is a placeholder until better effectivity data become available.

Latent Period

The length of the latent period and subsequent symptoms depend on the route of exposure. Little information is available on the latent period after inhalational ricin exposure. *MABW* states that in NHPs, the length of the latent period is dose dependent and ranges from 8 to 24 hours[1109] but cites a report that does not support the statement. The only comment in the original report referring to latent period is, "After a lag period of from 20 to 24 hours, monkeys had abrupt onset of dyspnea, which progressed rapidly."[1110] Rats reportedly have a similar latent period of 18 to 24 hours after inhaling ricin, but the authors of the report did not comment on dose dependence.[1111] Mice that inhaled lethal doses had symptoms onset after 30 hours, but "clinical signs in mice receiving lower doses were inconsistent."[1112]

[1106] Griffiths et al., "Inhalation Toxicology and Histopathology of Ricin," 277.
[1107] Ibid., Table 1.
[1108] M. Bhaskaran et al., "Pathology of Lethal and Sublethal Doses or Aerosolized Ricin in Rhesus Macaques," *Toxicology Pathology* 42, no. 3 (2014): 573–581.
[1109] Poli et al., "Ricin," 329.
[1110] Wilhelmsen and Pitt, "Lesions of Acute Inhaled Lethal Ricin," 297.
[1111] Griffiths et al., "Inhalation Toxicology and Histopathology of Ricin and Abrin Toxins," 277.
[1112] Catherine L. Wilhelmsen, *Inhaled Ricin Dose Ranging and Pathology in Inbred Strains of Mice* (Fort Detrick, MD: USAMRIID, June 2000), 7.

On the contrary, *MMBC* states that symptoms begin in humans 4 to 8 hours after inhalational exposures. But the only evidence provided is the following unreferenced sentence: "Accidental sublethal aerosol exposures, which occurred in humans in the 1940s, were characterized by onset of fever, chest tightness, cough, dyspnea, nausea, and arthralgias within 4 to 8 h."[1113] We were unable to locate any other report on these human exposures or any additional details of the exposures.

The latent period model is based on the statement in *MMBC* for three reasons:(1) human data are preferable to nonhuman data; (2) these data provide a more conservative casualty estimate; and (3) *MMBC* is considered a trustworthy source, and although its statement is unreferenced, the case-specific data from the animal experiments are equally unavailable—the reports only give general summary statements.

The latent period may be dose dependent, especially since the duration of illness is clearly dose dependent (see Subsection 0). However, until specific data on which to base a model become available, the model is a constant latent period. The length is 6 hours, which theoretically represents the median individual based on the estimate of 4 to 8 hours from *MMBC*. One final comment is that as long as the latent period is less than 1 day, different specific numbers of hours will not make a difference in the casualty estimate produced by *AMedP-7.5* because it reports with 1-day time resolution.

Injury Profile

The symptoms of ricin intoxication are nonspecific and therefore may be difficult to diagnose. Symptoms of ricin exposure are well documented in the literature but are dependent on the route of exposure, and most reports focus on routes of exposure other than inhalational. For example, Thomson examined changes in the blood after acute ricin exposure and documented detailed and potentially useful results, except that the route of exposure was intraperitoneal (IP).[1114] According to *MABW*, GI symptoms are the primary effect of ingestion exposure, and IM or subcutaneous injection causes local lymphoid necrosis, GI hemorrhage, and some other systemic symptoms. In contrast, the effects of inhalational exposure are primarily pulmonary, although some milder systemic symptoms may occur.[1115] *MMBC* provides some details that assist in defining the stages of the Injury Profile:

> Fever, chest tightness, cough, dyspnea, nausea, and arthralgias occur 4 to 8 h after inhalational exposure. Airway necrosis and pulmonary capillary

[1113] USAMRIID, *Medical Management of Biological Casualties*, 131.

[1114] John F. Thomson, "Some Observations on the Mechanism of Toxic Action of Ricin," *Journal of Pharmacology and Experimental Therapeutics* 100, no. 3 (1950): 370–381.

[1115] Poli et al., "Ricin," 327–329; Griffiths et al., "Inhalation Toxicology and Histopathology of Ricin," 287; Wilhelmsen and Pitt, "Lesions of Acute Inhaled Lethal Ricin," 297.

> leak resulting in pulmonary edema may occur within 18–24 h, followed by severe respiratory distress and death from hypoxemia in 36–72 h.[1116]

This quotation is the basis of the three-stage Injury Profile for non-survivors of ricin intoxication. Table 238 summarizes the profile for non-survivors, with some additional descriptors from *MABW*.[1117]

Table 238. Ricin Non-survivor Injury Profile

	Stage 1	Stage 2	Stage 3
S/S	Fever; chest tightness; cough; dyspnea; nausea; arthralgia	Pulmonary edema; interstitial and alveolar inflammation; cyanosis; worsening cough	Diffuse necrotizing pneumonia; hypoxemia; acidosis; alveolar flooding
S/S Severity	1 (Mild)	3 (Severe)	4 (Very Severe)

For sublethal exposures, Stage 1 is the same as for lethal exposures. However, rather than progressing to pulmonary edema, "the onset of profuse sweating some hours [after the onset of Stage 1] was commonly the sign of termination of most of the symptoms."[1118] No other information on this second stage of the illness is available. If the original reports on determination of LD_{50} in monkeys become available, these reports may have information on the clinical course of the survivors. Given the information available, the Injury Profile for survivors of a ricin attack is modeled with two stages, as summarized in Table 239.

Table 239. Ricin Survivor Injury Profile

	Stage 1	Stage 2
S/S	Fever; chest tightness, cough; dyspnea; nausea; arthralgia	Profuse sweating; progressively milder versions of symptoms from Stage 1
S/S Severity	1 (Mild)	1 (Mild)

Duration of Illness

MMBC states that death will occur after 36–72 hours,[1119] but does not give a basis for the numbers. A model proposed by Anno covers both survivors and non-survivors with a probabilistic model.[1120] For non-survivors, the time until death is lognormally distributed

[1116] USAMRIID, *Medical Management of Biological Casualties*, 129.
[1117] Poli et al., "Ricin," 328–329.
[1118] USAMRIID, *Medical Management of Biological Casualties*, 131.
[1119] Ibid., 129.
[1120] George H. Anno, *Ricin Toxicity* (Arlington, VA: Pacific Sierra Research Corporation, April 2003), Table 2.

between 36 and 81 hours, with a median of 54 hours. For survivors, the estimated time of recovery to no symptoms is given as 192 hours (8 days), without a distribution.

The document discussing this model does not provide specific references or describe the derivation of the model and ignores the dose dependence of the survival time that is displayed in animals in the literature. Thus, it is useful only as a last resort, under the assumption that the model is based on some real data.

For time until death in non-survivors, the literature provides better information. Figure 15 summarizes the results from studies of ricin inhalation in rats, mice, and monkeys, with the dose (*x*-axis) converted to micrograms (µg) and allometrically scaled to human weight (70 kg). The results from three difference species align rather well and indicate an inverse relationship between dose and time to death. Table 240 lists the data plotted in Figure 15.

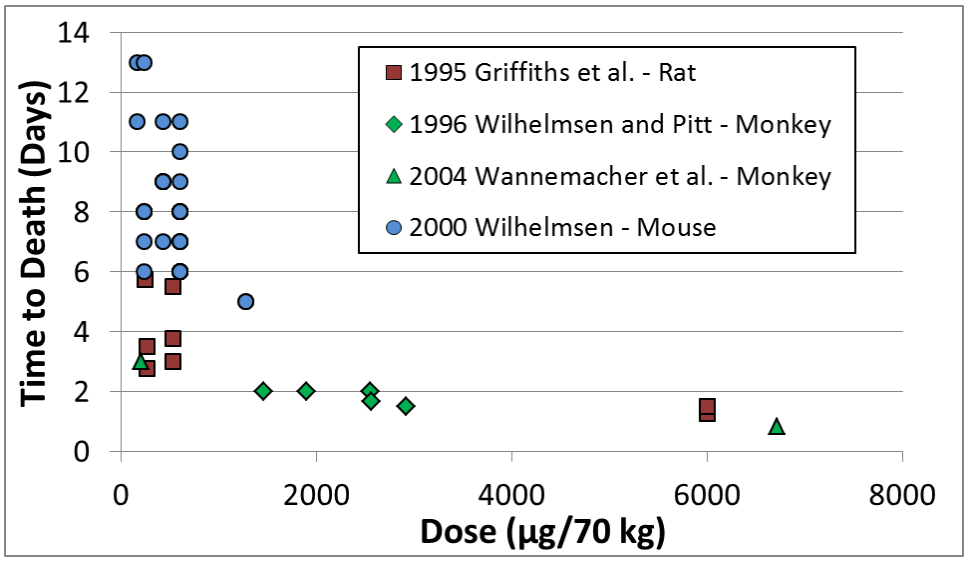

Figure 15. Time to Death in Three Species After Inhaling Ricin

Since we prefer NHP data over other animal data, we used the NHP data plotted in Figure 15 for development of the duration of illness model. The negative aspect of this approach is that in this case, we only have seven data points from NHPs. Although the NHP data alone may look more linear, we chose a power function to fit the data, given the shape of the total dataset. The fit to the NHP data is as follows:

$$\text{Days from exposure until death} = 19.4 \times (\text{dose in } \mu g)^{-0.3}.$$

Table 240. Time to Death in Three Species After Inhaling Ricin

Source	Animal Model	Reported Dose (µg/kg)	Time to Death (Days)
Griffiths et al.	Rat	85.8	1.3, 1.5 (*n* = 3)
		7.7	3.0, 3.8, 5.5
		3.8	2.8, 3.5 (*n* = 2)
		3.6	5.8
Wilhelmsen and Pitt	RM	41.8	1.5
		36.6	1.7
		36.5	2.0
		27.2	2.0
		21.0	2.0
Wannemacher et al., 2004	AGM	96.0	0.8
		3.0	3.0
Wilhelmsen	Mouse	18.2	5.0 (*n* = 2)
		8.6	6.0 (*n* = 6), 7.0 (*n* = 3), 8.0 (*n* = 5), 9.0, 10.0, 11.0
		6.2	7.0, 9.0 (*n* = 4), 11.0
		3.4	6.0, 7.0, 8.0 (*n* = 3), 13.0
		2.4	11.0, 13.0

Note: See Appendix B for full reference citations.

For the duration of specific symptoms and the duration of recovery for survivors, significantly less information on which to base a model is available in the literature. A quotation given in the previous section, from *MMBC* and repeated here, may be useful despite being unreferenced by the source:

> Fever, chest tightness, cough, dyspnea, nausea, and arthralgias occur 4 to 8 h after inhalational exposure. Airway necrosis and pulmonary capillary leak resulting in pulmonary edema may occur within 18-24 h, followed by severe respiratory distress and death from hypoxemia in 36-72 h.[1121]

The times listed in the quotation are consistent with the ranges listed in Anno's model: the acute phase ends between 12 and 24 hours (median 17), the terminal phase ends between 24 and 36 hours (median 29), and death occurs between 36 and 81 hours (median 54). Since time to death is dose dependent (see Figure 15), it is reasonable to assume that the progression through the earlier stages of disease is also dose dependent. Anno's model can serve as the source of the *ratio* between other important times (the ends of Stages

[1121] USAMRIID, *Medical Management of Biological Casualties*, 129.

1 and 2 for non-survivors and survivors) and the time to death, with the fit of the NHP data serving as the basis of comparison for the implementation of the ratios into the model.

In Anno's model for non-survivors, the median time to the end of the first stage is 31.5% of the time until death, and the median time to the end of the second stage is 53.7% of the time until death. Applying these ratios to the time to death model from the NHP data gives the following model of the duration of illness for non-survivors:

$$\text{Days from exposure until end of Stage 1} = 6.1\times(\text{dose in } \mu g)^{-0.3},$$

$$\text{Days from exposure until end of Stage 2} = 10.4\times(\text{dose in } \mu g)^{-0.3}, \text{ and}$$

$$\text{Days from exposure until death} = 19.4\times(\text{dose in } \mu g)^{-0.3}.$$

Similarly, in Anno's model for survivors, the median time to the beginning of recovery, which we assumed to be the end of Stage 1 for survivors, is 53.7% of the time until death for non-survivors, and the time until the end of Stage 2 (recovery) is fixed at 8 days. Combining Anno's model with the NHP data yields the following duration of illness model for survivors:

$$\text{Days from exposure until end of Stage 1} = 10.4\times(\text{dose in } \mu g)^{-0.3}, \text{ and}$$

$$\text{Days from exposure until end of Stage 2} = 8 \text{ days}.$$

Medical Countermeasures and Treatment Model

Although there is ongoing research effort to develop a ricin vaccine, and the candidate has been through two phase 1 trials,[1122] it has not completed the other trials needed, so it is not FDA-approved.

Supportive care is the only medical treatment for ricin intoxication. Supportive care for ricin is similar to supportive care for chemical agents that affect the pulmonary system: respiratory support to counteract acute pulmonary edema and respiratory distress. More specifically, "Positive-pressure ventilator therapy, fluid and electrolyte replacement, anti-inflammatory agents, and analgesics would likely be of benefit in treating the aerosol-exposed patient."[1123] Because there are no recorded cases of medical treatment of a human who inhaled ricin, there are no data on which to base a modification to the untreated models; the treated model is no different from the untreated model.

[1122] Soligenix, "RiVax™ Ricin Toxin Vaccine", accessed 10 May, 2016, http://www.soligenix.com/pipeline/vaccinesbiodefense/rivax-ricin-toxin-vaccine/.

[1123] Poli et al., "Ricin," 331.

Model Summary

Table 241, Table 242, and Table 243 summarize the model parameters for ricin intoxication in *AMedP-7.5*. While the parameters in these tables represent current best estimates, any new data that become available, particularly for inhalational exposure in humans or nonhuman primates, might significantly improve the model.

Table 241. Ricin Model Parameters Summary Table

Submodel	Type	Parameters
Effectivity	Lognormal distribution	ED_{50} = 120 µg Probit slope = 6.1 probits/log (dose)
Lethality	Lognormal distribution	LD_{50} = 343 µg Probit slope = 6.1 probits/log (dose)
Latent Period	Constant	6 hours
Duration of Illness		Dose-dependent
• Non-survivors		
Stage 1	Power function	c = 6.1, r = –0.3 (range: 1–4 days)
Stage 2	Power function	c = 4.3, r = –0.3 (range: 1–6 days)
Stage 3	Power function	c = 9.0, r = –0.3 (range: 1–10 days)
• Survivors	Constant	8 days
Stage 1	Power function	c = 10.4, r = –0.3 (range: 1–6 days)
Stage 2	Variable	8 days minus the length of Stage 1

Table 242. Ricin Non-survivor Injury Profile

	Stage 1	Stage 2	Stage 3
S/S	Fever; chest tightness; cough; dyspnea; nausea; arthralgia	Pulmonary edema; interstitial and alveolar inflammation; cyanosis; worsening cough	Diffuse necrotizing pneumonia; hypoxemia; acidosis; alveolar flooding
S/S Severity	1 (Mild)	3 (Severe)	4 (Very Severe)

Table 243. Ricin Survivor Injury Profile

	Stage 1	Stage 2
S/S	Fever; chest tightness, cough; dyspnea; nausea; arthralgia	Profuse sweating; progressively milder versions of symptoms from Stage 1
S/S Severity	1 (Mild)	1 (Mild)

Cohorts and Special Considerations (*AMedP-7.5 Section 5.2.15.3*)

Cohort populations are calculated according to the standard equations for E, F, and S in *AMedP-7.5* and then split based on dose ranges; no further explanation is warranted.

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1.32. SEB Intoxication Model (*AMedP-7.5 Section 5.2.16*)

Introduction

Staphylococcal enterotoxin B (SEB) is secreted by the gram-positive bacteria *Streptococcus pyogenes* and *Staphylococcus aureus*. SEB is one of the class of bacterial products called "superantigens" because of their profound effects upon the immune system:

> Most strains of *S. aureus* and *S. pyogenes* examined harbor genes for superantigens and are likely to produce at least one of these products. The staphylococcal enterotoxins are most frequently associated with food poisoning, yet not all superantigens are enterotoxins, and more severe physiological consequences, such as a life-threatening toxic shock syndrome (TSS), may result from exposure to any of the superantigens through a nonenteric route.[1124]

The pulmonary form of SEB intoxication that results from inhaling the aerosol form results in a markedly different clinical syndrome than if the toxin is ingested. SEB, not generally thought of as a lethal agent, is classified as an incapacitant. However, inhalational SEB intoxication can seriously debilitate humans, causing various degrees of performance decrement for a week or more depending on the inhaled dose and individual variability.[1125] High-dose, microgram-level exposures to SEB will result in fatalities, and inhalation exposure to nanogram or lower levels may be severely incapacitating.[1126]

Assumptions (*AMedP-7.5 Section 5.2.16.2*)

> **Assumption**: All individuals weigh 70 kilograms.

This assumption is necessary because the toxicity data are based on experimental data in human males and have been scaled to a weight of 70 kg.

> **Assumption**: The lethality probit slope is equal to the effectivity probit slope.

See Subsection 0.

[1124] Robert G. Ulrich, Catherine L. Wilhelmsen, and Teresa Krakauer, "Staphylococcal Enterotoxin B and Related Toxins," chap. 14 in *Medical Aspects of Biological Warfare*, ed. Zygmunt F. Dembek, *Textbook of Military Medicine* (Washington, DC: Department of Defense, Office of the Surgeon General, U.S. Army, Borden Institute, 2007), 312.

[1125] Anno et al., *AMedP-8* (*Biological*) *Methods Report*," 13.

[1126] Ulrich, Wilhelmsen, and Krakauer, "Staphylococcal Enterotoxin B and Related Toxins," 312.

Human Response Model (*AMedP-7.5 Tables 5-129 and 5-130*)

Literature Summary

In addition to *MABW*[1127] and the *P-8 BMR*,[1128] we relied heavily on infectivity and lethality studies published in a previously classified reference and clinical descriptions of the symptoms of nine victims of accidental exposure to aerosolized SEB described in:

- "Joint CB Technical Data Source Book, Volume VI, Toxin Agents, Part Two: Agent PG (U)" (Deseret Test Center, Fort Douglas, Utah, February 1973).
  - Hereafter referred to in main text as the *Sourcebook*.
- Sidell, Sheldon, "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 (Ft. Detrick, Frederick, MD, April 1965).

Combined, the above sources included human dose response data from animal exposure studies, military research volunteers (MRV), and accidental exposures. The Sidell report includes clinical descriptions of the symptoms of nine accidental exposure victims (also referenced in *MABW* and the *P-8 BMR*). Rusnak et al.[1129] discuss clinical records for additional accidental exposure cases (up to seven more inhalational cases), but those cases were not described at the level of clinical detail available in Sidell and required for the development of the SEB submodels. Although we requested to review the records for the additional cases described by Rusnak et al., we have not yet received permission.

It is clear that more data exist than what we reviewed in preparing this chapter, and these data should be reviewed to validate or update the models and parameters in this chapter for modeling and simulation of human response and casualty-estimation planning. In particular, there are very little human dose-response data across the full range of doses from ineffective to supra-lethal. This lack of data leads to potentially weak models for effectivity, lethality, latent period, and disease duration, where the models may not properly account for dose dependence. Since we recently gained access to the MRV records, we hope to be able to rectify the lack of data for the next version of *AMedP-7.5*. Alternatively, there seem to be very good (if limited) data for the signs and symptoms

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[1127] Ulrich, Wilhelmsen, and Krakauer, "Staphylococcal Enterotoxin B and Related Toxins," 311–322.

[1128] Anno et al., *AMedP-8* (*Biological*) *Methods Report*." As with Q fever and tularemia, although we did gain access to the clinical records for the MRVs in early 2016, we did not have time to analyze the data found therein before the completion of this technical reference manual. Thus, we rely on the data presented in the *P-8 BMR*.

[1129] J. M. Rusnak et al., "Laboratory Exposures to Staphylococcal Enterotoxin B," *Emerging Infectious Diseases* 10 (2004): 1544–1549.

resulting from inhalation of SEB, which enhances our confidence in the proposed Injury Profile submodel.

Effectivity

The *Sourcebook* provides raw data for respiratory exposure of humans to SEB (see Table 244), but the description of the experiment is not provided.[1130] The total dose received is based upon an agent purity of 95% to 99%.

Table 244. Human Respiratory Challenge Data for SEB

Total Dose Received (µg)	# Humans Challenged	# Humans Ill	% Response
0.001	4	0	0%
0.003	2	0	0%
0.01	2	0	0%
0.02	8	4	50%
0.03	8	4	50%
0.05	8	6	75%

Source: "Joint CB Technical Data Source Book, Agent PG," 3-4.

Probit analysis of these data provides the following results: ED_{50} of 0.026 µg with 95% confidence interval (CI) of 0.004 to 0.066 µg, and a PS of 2.54 with 95% CI of 0.17 to 4.91. The point estimates correspond with those found in the *Sourcebook*[1131] and many open literature sources, including the *P-8 BMR*,[1132] and are the values used in *AMedP-7.5*.

Lethality

Obviously, no lethality studies have been conducted on humans, but the *Sourcebook* does cite several lethality experiments on RMs. To derive various estimates of the human respiratory LD_{50}, the *Sourcebook* employs the assumption that the ratio of the RM respiratory ED_{50}(fever), or $RRFED_{50}$, to the RM respiratory LD_{50}, or $RRLD_{50}$, equals the analogous ratio in humans (ratio of the human respiratory ED_{50}(fever),[1133] to the human respiratory LD_{50}).[1134] The $RRFED_{50}$ was not available, but the analogous RM respiratory emesis-diarrhea ED_{50}, or $RREDED_{50}$, and the corresponding RM intravenous fever and emesis-diarrhea ED_{50}s, or $RIVFED_{50}$ and $RIVEDED_{50}$ were. Thus, the *Sourcebook*

1130 In providing the data, the *Sourcebook* refers to an interim technical report, a memorandum for the record, and a summary report, none of which were available to us.
1131 "Joint CB Technical Data Source Book, Agent PG," 3-4.
1132 Anno et al., *AMedP-8* (*Biological*) *Methods Report*," 94.
1133 As this is the value derived for the infectivity model, it will simply be referred to as the ED_{50}.
1134 As the purpose of this section is to derive this value, it will simply be referred to as the LD_{50}.

estimates the $RRFED_{50}$ according to Equation 21, and subsequently the human respiratory LD_{50} according to Equation 22.[1135]

$$\frac{RRFED_{50}}{RREDED_{50}} = \frac{RIVFED_{50}}{RIVEDED_{50}}$$

$$RRFED_{50} = RREDED_{50} \times \frac{RIVFED_{50}}{RIVEDED_{50}} = 18.3\mu g \times \frac{0.05\mu g}{0.78\mu g} = 1.17\mu g \quad (21)$$

$$\frac{RRFED_{50}}{RRLD_{50}} = \frac{ED_{50}}{LD_{50}}$$

$$LD_{50} = ED_{50} \times \frac{RRLD_{50}}{RRFED_{50}} = 0.026\ \mu\ g \times \frac{75\mu g}{1.17\mu g} = 1.66\mu g \quad (22)$$

As for a PS, the *Sourcebook* cites the source "Interim Summary of Staphylococcal Enterotoxin Program Investigations from July 1964 to Present," dated April 1966 (reference not available to us), and lists a value of 3.0 probits/log (dose) without any further explanation. Since the provenance of this number is not known, and since we are aware that numbers such as this were sometimes produced as a result of "expert judgment," we prefer to use the PS from the effectivity model, or 2.54 probits/log (dose). Although we are aware that there are issues with applying an effectivity PS to a lethality PS since the mechanism of "effect" is likely different from the mechanism of death, we still prefer this value because its origin can at least be traced to available sources.

Latent Period

The best data for estimating the duration of the latent period come from a case of nine individuals who were exposed to SEB in a 1964 laboratory accident. Both *MABW* and a specific report by Dr. Sheldon Sidell[1136] provide data on the incident.

Before discussing the data from the data report, we note that there is wide consensus that the latent period for SEB is on the order of *hours*, not days, and that since the time resolution for reporting in *AMedP-7.5* is 1 day, the exact number of hours makes no difference in the casualty estimate. For a similar reason, we did not attempt to derive a dose-dependent model of the latent period, even though sources such as the *Sourcebook* indicate that the latent period is likely dose-dependent.[1137]

[1135] Most of this paragraph, Equations 21 and 22, and the values in the equations, are taken from "Joint CB Technical Data Source Book, Agent PG," 3-5 and 4-3, with some minor changes to notation.

[1136] Sidell, "Human Clinical Syndrome."

[1137] "Joint CB Technical Data Source Book, Agent PG," 3-6.

From the Sidell report, it is possible to estimate the time of onset of various symptoms. However, Sidell notes that exposure occurred during one or both of the periods of animal exposure (0900–1030 hours and 1300–1430 hours), but the exact time for any individual is uncertain.[1138] The *MABW* chapter provides an estimate of the latent period for various symptoms, and we also produced a separate estimate by assuming all exposures occurred at 0900 (see Table 245).

Table 245. SEB Symptom Onset Time Estimates (hours post-exposure)

	IDA Analysis of Sidell Report				*MABW* Analysis of Sidell Report[c]			
Symptom	**Avg**	**SD**	**Min**	**Max**	**Avg**	**SD**	**Min**	**Max**
Cough	9.09	5.75	1	19.75	10.4	5.4	NR[a]	NR[a]
Elevated Temperature[b]	12.97	2.81	10.5	19.75	12.4	3.9	8.0	20.0
Chills	9.44	2.26	7	12	NR[a]	NR[a]	NR[a]	NR[a]
Headache	9.47	4.64	5	19.75	13.3	10.0	4.0	36.0
Nausea	13.38	6.81	7	23.75	17.0	6.3	8.0	24.0
Myalgia	10.75	3.50	7	15	13.0	5.0	8.0	20.0
Malaise	11.59	4.34	7	19.75	NR[a]	NR[a]	NR[a]	NR[a]
Chest Pain	9.00	1.90	7	12	12.0	6.5	NR	NR
Vomiting	13.17	6.01	7	19	14.0	5.1	8.0	20.0
Anorexia	14.88	6.73	7	23.75	18.5	5.6	8.0	24.0
Dyspnea	19.50	24.39	7	63	NR[a]	NR[a]	NR[a]	NR[a]

[a] NR = not reported

[b] IDA analysis based on temperature chart from Sidell report. It is not clear if the *MABW* value is based on the same, or based on a separately reported symptom of "feverish" in the Sidell report.

[c] Ulrich, Wilhelmsen, and Krakauer, "Staphylococcal Enterotoxin B and Related Toxins," 317.

Based on Table 245, one could estimate a range of different times for the latent period, almost all of which are practically equivalent to "1 day" in terms of how they would be used for *AMedP-7.5*. Since 9 hours is the lowest *average* value among the symptoms in the IDA analysis, however, we chose a value of 9 hours. If we had instead assumed the exposures occurred at 1430 (the latest time in the range), this estimate would change to 3.5 hours, which would make no difference for the purpose of *AMedP-7.5*.

Injury Profile

The nine accidental exposure cases exhibited, to varying degrees, fever, chills, malaise, myalgia, anorexia, nausea, vomiting, headache, chest pain, cough (productive

[1138] Sidell, "Human Clinical Syndrome," 25.

and/or nonproductive), and dyspnea. Rusnak et al. considered these 9 cases with 7 others and reported on the frequency with which these symptoms occurred in the 16 cases, shown in Table 246.

Table 246. Incidence of Signs and Symptoms Among Accidental Laboratory Exposures

Sign or Symptom	Incidence (%)[a]
Cough	15/16 (93.7)
Fever	15/16 (93.7)
Chills	13/16 (81.3)
Headache	13/16 (81.3)
Nausea	12/16 (75.0)
Myalgia	11/16 (68.7)
Malaise	9/14 (64.3)
Chest pain	8/14 (57.1)
Vomiting	9/16 (56.3)
Anorexia	9/16 (56.3)
Dyspnea	8/16 (50.0)

[a] Some of the cases had no data reported for some symptoms, thus the denominator may be less than 16.

From this, it is clear that the common signs and symptoms of inhalational SEB intoxication include cough, fever, chills, headache, nausea, myalgia, malaise, chest pain, vomiting, anorexia and dyspnea. Note that *MABW* does not include chills, malaise, or dyspnea on the list of common SEB signs and symptoms.[1139] Many other symptoms, such as fatigue, wheezing, abdominal cramps, diarrhea, gas, hepatitis, pharyngeal injection, rhinorrhea, postnasal drip, or sinus congestion, sore throat, otitis, hoarseness, conjunctival injection, burning eyes, and flushed face, may also occur within hours of exposure.

The Injury Profile is broken into two stages (the second of which is CONV instead of Stage 2), with only survivors progressing to the CONV stage, and non-survivors becoming DOW at the end of Stage 1. Based on the symptoms in the laboratory cases, Stage 1 signs and symptoms include nausea, vomiting, chills, dyspnea, chest pain, myalgia, headache, anorexia, malaise, elevated temperature, and cough. Taken together, and as indicated by the necessity of hospital care in the accidental laboratory cases, the Injury Severity Level for Stage 1 is 3 (Severe).

[1139] Ulrich, Wilhelmsen, and Krakauer, “Staphylococcal Enterotoxin B and Related Toxins,” 317.

The accidental laboratory exposure cases were released from the hospital and provided minimal care at home while still having a nonproductive cough, so instead of "Stage 2" the second stage is labeled CONV and includes only the one symptom.

Although Stage 1 is not Injury Severity Level 4, non-survivors are modeled to die after it concludes. There could be a brief period of Severity Level 4 symptoms prior to death, but as a practical matter due to the lack of data on how long such a stage might last, we did not include it in the model.

Table 247. SEB Injury Profile

	Stage 1 (all)	CONV (survivors)
Signs and symptoms (S/S)	Cough, headache, chest pain, myalgia, elevated temperature, vomiting, nausea, and anorexia	Non-productive cough
S/S Severity	3 (Severe)	1 (Mild)

Duration of Illness

The same dataset from the nine accidental exposure cases can be used to estimate the duration of the signs and symptoms of SEB intoxication in survivors. Just as for the estimate of the latent period, it is possible to compare the values from an IDA analysis of the nine accidental exposure cases and the values reported in *MABW* (see Table 248).

Table 248. SEB Symptom Duration Estimates (hours)

	IDA Analysis of Sidell Report				*MABW* Analysis of Sidell Report[c]			
Symptom	**Avg**	**SD**	**Min**	**Max**	**Avg**	**SD**	**Min**	**Max**
Cough	223.84	140.38	51	515	92.0	41.0	NR[a]	NR[a]
Elevated Temperature[b]	69.86	25.80	39	124.5	50.0	22.3	12.0	76.0
Chills	12.37	9.22	5	32	NR[a]	NR[a]	NR[a]	NR[a]
Headache	40.03	16.77	10	56	30.6	19.0	8.0	60.0
Nausea	12.71	10.05	5	32	9.0	5.5	4.0	20.0
Myalgia	39.12	13.34	27	56	16.0	15.0	4.0	44.0
Malaise	66.41	32.73	29	123	NR[a]	NR[a]	NR[a]	NR[a]
Chest Pain	34.00	45.26	5	123	23.0	27.0	4.0	84.0
Vomiting	9.33	2.31	8	12	Reported as none ("single event")			
Anorexia	52.12	40.34	8	117.5	44.5	45.0	4.0	136.0
Dyspnea	25.50	20.25	3	56	NR[a]	NR[a]	NR[a]	NR[a]

[a] NR = not reported

[b] IDA analysis is based on the temperature chart from the Sidell report. It is not clear if the *MABW* value is based on the same, or based on a separately reported symptom of "feverish" in the Sidell report.

[c] Ulrich, Wilhelmsen, and Krakauer, "Staphylococcal Enterotoxin B and Related Toxins," 317.

The duration for which SEB is a manifest illness must be defined as a function of these signs and symptoms, but it is open to interpretation as to which specific signs or symptoms should be used. A review of the average duration of each symptom would seem to group the symptoms into separate sets: nausea, vomiting, and chills endure 5 to 32 hours, with an average duration of about 9–12 hours. Dyspnea, chest pain, myalgia, headache, anorexia, malaise, and elevated temperature endure 3 to 125 hours, with an average duration of about 1 to 3 days. It appears reasonable to group all these symptoms together as "Stage 1" of the disease, since some subset of the group of them together is what resulted in the cases being admitted to the hospital, and the release from the hospital was only made after all of these symptoms had cleared. Cough is the only symptom with an average duration (9.3 days) well in excess of 3 days, and cough is also the only symptom with which patients were discharged from the hospital.

Since fever is the longest lasting of the symptoms in the Stage 1 syndrome, we considered the *P-8 BMR* model of the duration of illness model, which is based on the duration of fever in MRVs and is reproduced in Equation 23 (units of measure given in brackets, Δt_f is duration of fever, D is dose of SEB). The *P-8 BMR* limits the equation to a maximum dose of 0.15 µg, which corresponds to about 60 hours (2.5 days), presumably to match the MRV data from which it was derived.

$$\Delta t_f[\text{hours}] = 371.4122 \left[\frac{\text{hours}}{\mu\text{g}}\right] \times D[\mu\text{g}] + 6.0966[\text{hours}] \tag{23}$$

We made a few changes to the above equation to better suit the model for use in *AMedP-7.5*. The first change is to account for a rounding issue caused by the 9-hour constant latent period. Specifically, since *AMedP-7.5*'s time resolution is 1 day, the 9-hour latent period is essentially rounded to 0 days—that is, individuals are declared WIA on Day 1, and the duration of illness "timer" therefore starts at Hour 0 (the beginning of Day 1). If Equation 23 is used as is, casualties will complete Stage 1 9 hours earlier than they really should. To fix this problem, we added 9 hours to the additive term. Note that this makes the specific choice of the fixed duration for the latent period even less consequential, since it is certainly less than 1 day, and whatever value was chosen would have been used to modify the duration of Stage 1 equation in this way. The second change to Equation 23 is to convert it to units of days, by dividing all terms by 24. Thus, the *AMedP-7.5* equation for calculating the duration of Stage 1 for survivors is given in Equation 24.

$$Dur_{Stg1-Survivor}[\text{days}] = 15.4755 \left[\frac{\text{days}}{\mu\text{ g}}\right] \times X_{SEB,n}^{eff}[\mu\text{g}] + 0.629[\text{days}] \tag{24}$$

What motivates the final change is that we know from the accidental laboratory exposures that Stage 1 symptoms can persist for longer and that there is effectively no limit on the doses one could plan against while using *AMedP-7.5*. Thus, we extended the equation to higher doses. Although there is no evidence that the functional form given in Equation 24 is suitable for higher doses, there are also no data to enable an assessment of whether the use to which we put Equation 24 in the next paragraph is or is not appropriate.

Since the LD_{50} is a factor of about 64 times higher than the ED_{50}, Equation 24 could theoretically be used to predict a Stage 1 duration of illness far longer than those that have been observed. For example, if the LD_{50} is used, the 50% of individuals who survived would be estimated to have a 26-day duration of Stage 1. However, the longest observed duration in the accidental cases for Stage 1 symptoms is about 5 days, consistent with *MABW*[1140] and Rusnak et al.[1141] Therefore, we used Equation 24 to develop dose ranges that correspond to completing Stage 1 on a certain day post-exposure, but only created dose ranges for days up to Day 7 (slightly longer than those observed because, since none of the historical cases ended in death, we can anticipate that the doses were not particularly high). The dose ranges and corresponding durations of survivor Stage 1 are shown in Table 249.

Table 249. *AMedP-7.5* SEB Dose Ranges and Corresponding Durations of Survivor Stage 1

Dose Range Label	Minimum Dose (µg)	Maximum Dose (µg)	Duration of Survivor Stage 1 (days)
A	0	0.0240	1
B	0.0240	0.0886	2
C	0.0886	0.1532	3
D	0.1532	0.2178	4
E	0.2178	0.2824	5
F	0.2824	0.3471	6
G	0.3471	(none)	7

As for the duration of the CONV period after Stage 1 ends, the best data available are again from the laboratory accident. Table 248 shows that the average duration of cough was 223.84 hours and the average duration of fever (representative of Stage 1) was 69.86 hours. Thus, the average duration post-fever one might expect cough to last is 153.98 hours, or about 6.5 days. We therefore set the duration of the CONV period equal to 7 days.

[1140] Ulrich, Wilhelmsen, and Krakauer, “Staphylococcal Enterotoxin B and Related Toxins,” 317.
[1141] Rusnak et al., “Laboratory Exposures to Staphylococcal Enterotoxin B,” 1547.

There are no data for human non-survivors of exposure to SEB, so we turned to NHP data. Soto and Roessler reported on experimental exposures of 30 RMs to varying doses of aerosolized SEB, of which 9 died naturally (not via euthanasia) between 53 hours and 72 hours post-exposure.[1142] Similarly, Tseng et al. report that when they dosed control RMs or RMs with low-level antibody protection with supralethal doses of aerosolized SEB, they died on Day 3 post-exposure.[1143] On the basis of these two papers, we set the duration of Stage 1 for non-survivors to 3 days, after which they become DOW.

Medical Countermeasures and Treatment Model

Medical management of SEB casualties focuses on supportive care. There are no vaccines or drugs available to prevent or treat SEB intoxication. Therefore, there is no treated model.

Model Summary

Table 250 and Table 251 summarize the model parameters for SEB used in *AMedP-7.5*. The model was derived primarily from a somewhat limited dataset on humans who inhaled aerosols of SEB and, when necessary, from experimental data on RMs that inhaled aerosols of SEB. Thus, these models could be improved only if additional human inhalation data become available.

Table 250. SEB Model Parameters Summary Table

Submodel	Type	Parameters
Infectivity	Lognormal distribution	ID_{50} = 0.026 µg Probit slope = 2.54 probits/log (dose)
Lethality	Lognormal distribution	LD_{50} = 1.66 µg Probit slope = 2.54 probits/log (dose)
Incubation period	Constant	9 hours
Duration of illness		
• Stage 1 (survivors)	Linear function	*m* = 15.4755 days/µg *b* = 0.629 days
• CONV (survivors)	Constant	7 days
• Stage 1 (non-survivors)	Constant	3 days

Table 251. SEB Injury Profile

[1142] Peter J. Soto, Jr. and William G. Roessler, *Staphylococcal Enterotoxemia: Pathologic Lesions in Rhesus Monkeys Exposed by Aerosol*, Technical Manuscript 226 (Frederick, MD: Army Biological Labs, September 1965), Table 1.

[1143] Jeenan Tseng et al., "Immunity and Responses of Circulating Leukocytes and Lymphocytes in Monkeys to Aerosolized Staphylococcal Enterotoxin B," *Infection and Immunity* 61, No. 2 (1993): Table 1.

	Stage 1 (all)	CONV (survivors)
Signs and symptoms (S/S)	Cough, headache, chest pain, myalgia, elevated temperature, vomiting, nausea, and anorexia	Non-productive cough
S/S Severity	3 (Severe)	1 (Mild)

Cohorts and Special Considerations (*AMedP-7.5 Section 5.2.16.3*)

Cohort populations are first calculated according to the standard equations for E, F, and S in *AMedP-7.5*. Then the S cohort is split into subcohorts based on the dose range. These procedures are sufficiently explained in *AMedP-7.5*, so no further explanation is warranted here.

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1.33. T-2 Mycotoxicosis Model (*AMedP-7.5 Section 5.2.17*)

Introduction

The trichothecenes are a large family of mycotoxins commonly found worldwide in cereal grains, animal feeds, and forages.[1144] Mycotoxins are toxic metabolites of fungi. Trichothecenes are produced by various species of *Fusarium*, *Myrothecium*, *Trichoderma*, *Cephalosporium*, and *Stachybotrys*.[1145] More than 150 trichothecenes have been identified, and among them, T-2 mycotoxin (T-2) is one of the most potent. It is produced by soil fungi of the *Fusarium* genus.[1146] As a toxin, its action on the body is more similar to chemical agents than to infectious agents. We modeled it as a noncontagious agent.

One interesting feature of T-2 mycotoxicosis is that many of the symptoms are independent of the route of exposure, but the LD_{50} and ED_{50} are dependent on the route of exposure. This phenomenon is also observed with nerve agents. *MABW* states, "By aerosol exposure, the lethality of T-2 toxin is 10 to 50 times greater than when it is injected parenterally"[1147] and indicates that effectivity qualitatively follows a similar trend. As for symptoms, the book notes:

> Once the trichothecene mycotoxins enter the systemic circulation, regardless of the route of exposure, they affect rapidly proliferating tissues. Oral, parenteral, cutaneous, and respiratory exposures produce (*a*) gastric and intestinal lesions; (*b*) hematopoietic and immunosuppressive effects described as radiomimetic in nature; (*c*) central nervous system toxicity resulting in anorexia, lassitude, and nausea; and (*d*) suppression of reproductive organ function as well as acute vascular effects leading to hypotension and shock.[1148]

The additional route-specific symptoms appear to be less significant than the systemic symptoms described in the quotation. Building on the case that the effects of T-2 are largely route independent, Creasia et al. used isotopic labeling to track the toxin in mice after

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[1144] C. F. Jelinek, A. E. Pohland, and G. E. Wood, "Worldwide Occurrence of Mycotoxins in Foods and Feeds – an Update," *Journal of the Association of Official Analytical Chemists* 72, no. 2 (1989):
223– 230.

[1145] Yoshio Ueno, "Toxicological Features of T-2 Toxin and Related Trichothecenes," *Fundamental and Applied Toxicology* 4, no. 2 (1984): S124–S132.

[1146] Maria A. Quiroga, Miguel A. Risso, and Carlos J. Perfumo, "T-2 Mycotoxin Intoxication in Piglets: A Systematic Pathological Approach and Apoptotic Immunohistochemical Studies," *Brazilian Journal of Veterinary Pathology* 2, no. 1 (2009): 16–22.

[1147] Kermit D. Huebner et al., "Additional Toxins of Clinical Concern," chap. 17 in *Medical Aspects of Biological Warfare*, ed. Zygmunt F. Dembek, Textbooks of Military Medicine (Washington, DC: OTSG, 2007), 356.

[1148] Ibid., 358.

inhalational exposure and found that at the end of the 10-minute exposure time, only 1% to 2% of the toxin remained in the respiratory tract, while the rest was distributed throughout the carcass.[1149] Supporting this finding, Creasia et al. also discovered no significant lesions in the upper respiratory tract. Marrs et al. found that the histological changes caused by inhalational and subcutaneous T-2 exposure in guinea pigs were similar to the changes observed by DeNicola et al.[1150] after dosing guinea pigs orally with T-2.[1151] Several other reports also show that aerosolized T-2 causes systemic symptoms without, or with only mild, pulmonary injury.[1152]

Given the systemic effects of T-2, it seems counterintuitive that the LD_{50} is lower for aerosol exposure than for other routes. The reason for the enhanced lethality by aerosol exposure is unknown. Regardless of the reason, for developing ED_{50} and LD_{50} estimates, inhalation data are clearly required. The importance of route of exposure for the latent period, Injury Profile, and duration of illness models is less clear, and we used some non-inhalational data out of necessity.

Assumptions (*AMedP-7.5 Section 5.2.17.2*)

Assumption: All individuals weigh 70 kilograms.

This assumption is necessary because the toxicity data for the lethality model have been scaled to a weight of 70 kg.

Assumption: The effectivity probit slope is equal to the lethality probit slope.

See Subsection 0.

[1149] Donald A. Creasia et al., "Acute Inhalation Toxicity of T-2 Mycotoxin in Mice," *Fundamental and Applied Toxicology* 8, no. 2 (1987): 230–235.
[1150] D. B. DeNicola et al., "T-2 Toxin Mycotoxicosis in the Guinea-Pig," *Food and Cosmetics Toxicology* 16, no. 6 (1978): 601–609.
[1151] T. C. Marrs et al., "Acute Toxicity of T2 Mycotoxin to the Guinea-Pig by Inhalation and Subcutaneous Routes," *British Journal of Experimental Pathology* 67, no. 2 (1986): 259–268.
[1152] D. A. Creasia et al., "Acute Inhalation Toxicity of T-2 Mycotoxin in the Rat and Guinea Pig," *Fundamental and Applied Toxicology* 14, no. 1 (1990): 54–59; D. A. Creasia and J. D. Thurman, "Comparative Acute Inhalation Toxicity of a Saline Suspension and an Ethanol Solution of T-2 Mycotoxin in Mice," *Inhalation Toxicology* 5, no. 1 (1993): 33–41; Victor F. Pang et al., "Experimental T-2 Toxicosis in Swine Following Inhalation Exposure: Effects on Pulmonary and Systemic Immunity, and Morphologic Changes," *Toxicology Pathology* 15, no. 3 (1987): 308–319.

Human Response Model (*AMedP-7.5 Tables 5-135 and 5-136*)

Literature Summary

Human Data

MABW mentions several cases of human exposure to trichothecene mycotoxins, most of which were by accidental ingestion or cutaneous exposure from contaminated hay or hay dust and involved toxins other than T-2. The only confirmed exposure to T-2 without concurrent exposure to other harmful substances of which we are aware occurred when a solution containing T-2 accidentally spilled inside the gloves of two laboratory workers.[1153] Because the workers washed their hands immediately, they only experienced dermal symptoms. The case shows that even after a dose low enough that no systemic toxicity occurs, severe cutaneous irritation lasts for about 2 weeks after exposure, but it cannot provide any other information for the submodels. No other human data from confirmed T-2 exposure are available.

Animal Data

Most of the animal studies on T-2 are from the 1980s and were pursued because of Cold War era threats. After the fall of the Soviet Union, interest in studying T-2 mycotoxin appeared to declined precipitously. The literature survey supporting this chapter did not locate any reports published after the early 1990s that provide new information useful for the submodel parameterization. Table 34-3 of *Medical Aspects of Chemical and Biological Warfare*, published in 1997, contains a summary of mammal testing with T-2.[1154] The table covers 7 species and 10 routes of exposure but does not cite any reports published later than 1991. As chemical and biological weapons specialist David R. Franz states, "aerosol toxicities are generally too low to make this class of toxins [trichothecene mycotoxins] useful to an aggressor as an MCBW [mass casualty biological weapon]."[1155]

Lethality

No human data are available for developing the lethality model. To estimate the LD_{50}, we used animal inhalation data exclusively. To estimate the PS, we also used data from IM-dosed NHPs because we could not find any NHP inhalation data.

Table 252 summarizes the reports of inhalation studies used for this analysis, along with the reported lethality parameters. Where possible, we conducted probit analysis using the raw data presented in the original reports to estimate the LD_{50} and the PS. Table 253 summarizes these results with confidence intervals. Table 254, Table 255, Table 256, and

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[1153] Heubner et al., "Additional Toxins," 359–361.

[1154] Robert W. Wannemacher and Stanley L. Wiener, "Trichothecene Mycotoxins," in *Medical Aspects of Chemical and Biological Warfare*, ed. Frederick R. Sidell, (Washington, DC: OTSG, 1997), 661.

[1155] David R. Franz, *Defense Against Toxin Weapons* (Fort Detrick, MD: U.S. Army Medical Research and Materiel Command, 1997), 20.

Table 257 present the raw data we used in our probit analyses. In the next two tables, the "exposure vehicle" is the liquid in which T-2 was dissolved or suspended. The discussion following the tables first focuses on an LD_{50} estimate and then turns to the PS.

Table 252. Reported Lethality Parameters for Various Animals after Inhaling T-2 Mycotoxin

Source	Animal Model	Exposure Vehicle	LD_{50} (mg/kg)	Probit Slope
Creasia et al., 1986	Rat	Ethanol	0.05	n/a[a]
Marrs et al.	Guinea Pig	Ethanol	N/A[b]	5.25
Creasia and Lambert	Swine	Ethanol	2.5	n/a[a]
——	Rat	Saline suspension	0.1	n/a[a]
——	Rat	Ethanol or dimethylsulfoxide (DMSO)	2.2	n/a[a]
——	Mouse	Saline suspension	0.16	n/a[a]
——	Mouse	Ethanol or DMSO	4.6	n/a[a]
Creasia et al., 1987	Young Mouse	Ethanol	0.24	n/a[a]
——	Mouse	Ethanol	0.94	n/a[a]
Creasia et al., 1990	Guinea Pig	Ethanol	0.4	n/a[a]
——	Rat	Ethanol	0.05	n/a[a]
Creasia and Thurman	Mouse	Saline suspension	0.3[c]	n/a[a]
——	Mouse	Ethanol	3.4[c]	n/a[a]

[a] The authors did not report a probit slope.

[b] The authors reported an LCt_{50} that cannot be converted to LD_{50} without assumptions on our part. Table 253 presents our analysis of their data.

[c] The authors reported an LC_{50} rather than LD_{50}. This is the equivalent LD_{50} based on the exposure duration and animal masses reported by the authors and on the respiratory minute volumes in Bide, Armour, and Yee, "Allometric Respiration/Body Mass Data," Table 6.

Note: See Appendix B for full refefence citations.

Table 253. Lethality Parameters for Various Animals after Inhaling T-2 Mycotoxin, Estimated by IDA

Source	Animal Model	Exposure Vehicle	LD_{50} (mg/kg) [95% CI]	PS (Probits/Log (dose)) [95% CI]
Marrs et al.	Guinea Pig	Ethanol	4.0 [2.9 – 5.8]	5.6 [1.7 – 9.5]
Creasia et al., 1987	Young Mouse	Ethanol	1.5 0.8 – 2.4]	1.5 [1.45 – 1.52]
	Mouse	Ethanol	2.4 [1.9 – 2.9]	3.8 [3.6 – 4.0]
Creasia et al., 1990	Guinea Pig	Ethanol	3.7 [2.5 – 5.0]	3.8 [3.2 – 4.4]
	Rat	Ethanol	0.4 [0.3 – 0.5]	3.5 [3.0 – 3.9]
Creasia and Thurman	Mouse	Saline suspension	0.4 [0.3 – 0.5]	3.1 [2.8 – 3.4]
	Mouse	Ethanol	3.2 [2.5 – 4.0]	3.7 [3.4 – 4.1]

Note: Where necessary because the authors did not report such data, we used the animal masses and minute volumes in Bide, Armour, and Yee, "Allometric Respiration/Body Mass Data," Table 6, to convert the units characterizing the exposure to mg/kg before performing probit analysis.

Note: See Appendix B for full reference citations.

Table 254. Data from Marrs et al., 1986 used in Probit Analysis

Dose (mg/kg)	Number of Rats (Dead/Exposed)
1.94	0/6
3.25	2/6
4.33	4/6
6.74	5/6

Table 255. Data from Creasia et al., 1987 Used in Probit Analysis

Aerosol Mass Concentration (mg/L)	Number of Young Mice Dead/Exposed	Aerosol Mass Concentration (mg/L)	Number of Adult Mice Dead/Exposed
0.003	0/12	0.1	0/12
0.017	3/12	0.15	1/12
0.040	3/12	0.2	3/12
0.23	7/12	0.3	5/12
0.35	8/12	0.5	7/12
0.4	10/12	0.7	10/12
0.5	12/12	1.1	12/12
0.7	12/12	1.3	12/12
1.5	11/12	1.5	12/12
1.8	12/12	2.4	12/12

Note: The concentrations were converted to dose (mg/kg) using an average “young” mass of 19.5 g (based on a range of 17–22 g reported by the authors); an average “mature” mass of 40 g (based on a range of 35–45 g reported by the authors); an exposure duration of 10 minutes; and a minute volume of 0.0269 L/min, as estimated by Bide, Armour, and Yee, “Allometric Respiration/Body Mass Data,” Table 6.

Table 256. Data from Creasia et al., 1990 Used in Probit Analysis

Aerosol Mass Concentration (mg/L)	Number of Rats Dead/Exposed	Aerosol Mass Concentration (mg/L)	Number of Guinea Pigs Dead/Exposed
0.001	0/12	0.025	0/6
0.01	2/12	0.075	1/6
0.02	5/12	0.15	0/6
0.03	8/12	0.25	3/6
0.05	11/12	0.3	3/6
0.1	12/12	0.4	5/6
1.0	12/12	0.66	6/6
		0.76	6/6
		0.92	6/6

Note: The concentrations were converted to dose (milligrams per kilogram (mg/kg)) using an average rat mass of 95 g (based on a range of 90–100 g reported by the authors); an average guinea pig mass of 195 g (based on a range of 190–200 g reported by the authors); an exposure duration of 10 minutes; and minute volumes of 0.17 and 0.297 L/min for rats and guinea pigs, respectively, as estimated by Bide, Armour, and Yee, “Allometric Respiration/Body Mass Data,” Table 6.

Table 257. Data from Creasia and Thurman, 1993 Used in Probit Analysis

T-2 Ethanol Solution		T-2 Saline Suspension	
Aerosol Mass Concentration (mg/L)	Number of Rats Dead/Exposed	Aerosol Mass Concentration (mg/L)	Number of Guinea Pigs Dead/Exposed
0.1	0/12	0.02	0/12
0.2	3/12	0.03	2/12
0.3	5/12	0.04	7/12
0.5	7/12	0.07	10/12
0.7	10/12	0.1	12/12
1.1	12/12	0.15	12/12
1.5	12/12	0.5	11/12
		1.0	12/12

Note: The concentrations were converted to dose (milligrams per kilogram (mg/kg)) using an average mouse mass of 30 g (as reported by the authors); an exposure duration of 10 minutes; and a minute volume of 0.0269 L/min, as estimated by Bide, Armour, and Yee, “Allometric Respiration/Body Mass Data,” Table 6.

Creasia et al. (1987) compared the acute inhalation toxicity of T-2 in young adult mice to that in adult mice. The data show that T-2 is at least twofold more lethal to young adult mice than to adult mice.[1156] In 1990, Creasia et al. similarly showed that T-2 is tenfold more lethal to rats than guinea pigs.[1157] An explanation of the apparently high sensitivity of young mice and rats remains to be determined. We excluded data from young mice and rats from further analysis because there is no reason to believe that humans have particularly high sensitivity to T-2.

Table 252 and Table 253 show that the LD_{50} for inhalation of T-2 dissolved in ethanol is similar for swine, guinea pigs, and mice—animals from as small as tens of grams up to tens of kilograms. Thus, among these choices for T-2, it likely makes little difference which animal model is chosen as the data source for scaling the LD_{50} to human mass. However, a different feature (i.e., the importance of the "exposure vehicle") of the data appears to be very important.

The exposure vehicle is a critical factor in determining the LD_{50}.[1158] From Table 252 and Table 253, it is clear that T-2 in a saline suspension is several times more lethal than T-2 dissolved in ethanol. The reason for the enhanced toxicity of suspended T-2 relative to dissolved T-2 is unknown. Since solvents tend to evaporate quickly, one possible explanation is different particle size distributions after the solvents evaporated.

Whatever the reason for the enhanced toxicity, it undoubtedly exists in rats and mice. It seems reasonable to assume that this enhanced toxicity also exists in humans, given the absence of data to confirm or deny. Therefore, T-2 suspended in saline is the more likely choice for weaponized T-2[1159] and should be the basis of the LD_{50} for the model.

The two reported LD_{50}s for mice exposed to T-2 suspended in saline are 0.16 and 0.3 mg/kg. From the raw data provided by Creasia and Thurman, we calculated an LD_{50} of 0.4 mg/kg and a PS of 3.1 probits/log (dose). On this basis, the model uses an LD_{50} of 0.4 mg/kg× 70 kg = 28 mg. The PS requires further consideration because some NHP data are available for the PS.

The available PS data from an NHP experiment comes from Bunner et al., who gave IM doses to monkeys. Because the route of exposure was not inhalation, the LD_{50} is not considered; however, since PSs represent variance within the animal species and agent and most of the damage caused by T-2 mycotoxicosis is not route dependent, we assume the

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[1156] Creasia et al., "Acute Inhalation Toxicity of T-2 Mycotoxin in Mice," 234.

[1157] Creasia et al., "Acute Inhalation Toxicity of T-2 Mycotoxin in the Rat and Guinea Pig," 58.

[1158] Creasia and Lambert, *Acute Respiratory Tract Toxicity*; Creasia and Thurman, "Comparative Acute Inhalation Toxicity."

[1159] Assuming it is technically feasible to deliver a widespread cloud via this method.

PS does not vary with route of exposure. Bunner et al. report an LD_{05} of 0.31 mg/kg.[1160] They also report LD_{50} of 0.8 mg/kg, but a later book chapter written by some of the same authors states that the LD_{50} was 0.75 mg/kg.[1161] It follows from an LD_{05} of 0.31 mg/kg and an LD_{50} of 0.75 mg/kg that the PS is 4.3 probits/log (dose), which is generally consistent with the values in Table 253. Because this PS is the only one derived from NHP data, it is the preferred value for the model.

Effectivity

Only one of the six reports on inhalation testing listed in Table 252 provides data on effectivity. None of the available effectivity data can be used for estimating an effectivity PS. We therefore assumed that the PS from the lethality model described previously could be applied to effectivity. Likewise, we assumed that the PSs for lethality and effectivity are equal within other species and used this assumption to assist in the development of an ED_{50} estimate.

The section of Creasia and Lambert's report on swine briefly discusses sublethal inhalation exposures that produced signs and symptoms of exposure. They state that a dose of approximately 2 mg/kg was required (assumed to mean minimum effective dose, ~ED_{01}) to produce clinical signs without subsequent lethality and that deaths began to occur (assumed to mean minimum lethal dose, ~LD_{01}) with doses of approximately 2.5 mg/kg.[1162] They did not provide the raw data used to generate these estimates. Some assumptions are necessary to make this information usable for the effectivity model. A consequence of assuming the PSs for effectivity and lethality are equal is that $ED_{01}/LD_{01} = ED_{50}/LD_{50}$. Thus, the estimated ratio of ED_{50}/LD_{50} for T-2 inhalation in swine is $2.0/2.5 = 0.80$.

Since so little inhalational effectivity data are available, we also considered non-inhalational data. Because the LD_{50} (and presumably also the ED_{50}) is known to vary by at least one order of magnitude between different routes of exposure, only reports that provided enough information to determine the ED_{50}/LD_{50} ratio from experiments by the same group were considered potentially useful—again, under the assumption that the ratio is the same for different species. With this restriction, three non-inhalational datasets provided the necessary data.

[1160] David L. Bunner et al., "Pathophysiology of Acute T-2 Intoxication in the Cynomolgus Monkey and Rat Models," in *Trichothecenes and Other Mycotoxins*, ed. J. Lacey (Chichester, England: John Wiley & Sons Ltd., 1985), 413.

[1161] Robert W. Wannemacher, David L. Bunner, and Harold A. Neufeld, "Toxicity of Trichothecenes and Other Related Mycotoxins in Laboratory Animal," in *Mycotoxins and Animal Foods*, ed. J. E. Smith and R. S. Henderson (Boca Raton, FL: CRC Press, 1991), 522.

[1162] Creasia and Lambert, *Acute Respiratory Tract Toxicity*, 13–14.

In the first of the three non-inhalation studies, DeNicola et al. report on gastric intubation of T-2 into guinea pigs, including enough information to construct effectivity and lethality probit curves from the same set of experiments.[1163] Table 258 summarizes their data, and Table 259 gives the results of our probit analysis of their data.

Table 258. Effectivity and Lethality Data from DeNicola et al.

Dose (mg/kg)	Number Ill/Exposed	Number Dead/Exposed
1.85	1/5	1/5
2.52	2/5	1/5
3.43	5/5	3/5
4.66	5/5	5/5

Table 259. Results of IDA Dose-Response Analysis of Data from DeNicola et al.

Degree of Effect	Median Dose (mg/kg) [95% CI]	PS Probits/Log (dose) [95% CI]
Effective	2.4 [1.8 – 3.1]	10.0 [0 – 25.2]
Lethal	2.9 [2.1 – 4.0]	6.6 [0.4 – 12.9]

That the PSs are not equal conflicts with our assumption in the first paragraph of this section but may simply be the result of having so few data points on which to base the probit analysis. Given the wide 95% CIs, there is no statistically significant conflict. The usable information from DeNicola et al. is that the ratio ED_{50}/LD_{50} is 2.4/2.9, or 0.83, which is consistent with the ratio derived from swine data.

In the second of the three non-inhalation studies, Fairhurst et al. state, "T2 caused vomiting in pigeons at doses of one fifth or less the LD_{50}"[1164] and note that emesis is the first sign in pigeons, whereas other commonly used animals for T-2 testing cannot vomit and therefore may not be ideal for testing the effectivity. This pigeon ED_{50}/LD_{50} ratio of 0.2 is significantly different from the ratios from swine and guinea pigs. The authors did not provide the underlying data needed to confirm their result. Since pigs are capable of vomiting, there is no obvious explanation for the difference aside from the fact that pigs

[1163] DeNicola et al., "T-2 Toxin Mycotoxicosis," 602.

[1164] S. Fairhurst et al., "Acute Toxicity of T2 Toxin in Rats, Mice, Guinea Pigs, and Pigeons," *Toxicology* 43, no. 1 (1987): 31.

are a different species. Perhaps the more relevant question is whether inhalational dosing of swine better represents a human inhalational model than sublingual dosing of pigeons. We believe that it does and therefore disregarded the pigeon data.

The third non-inhalation source states that the IM minimum effective dose for monkeys (interpreted as ED_{05} based on the description in the book) is 0.25 mg/kg.[1165] We derived the PS of 4.3 probits/log (dose) for the lethality model from IM monkey data. Applying the same slope to the effectivity data point that ED_{05} is 0.25 mg/kg, the estimated ED_{50} is 0.61 mg/kg. The monkey IM LD_{50} that contributed to the derivation of the PS is 0.75 mg/kg. Thus, the ratio of ED_{50}/LD_{50} for IM dosed monkeys is 0.61/0.75 = 0.81, which agrees well with the swine inhalation and guinea pig gastric intubation data.

To summarize the previous discussion: swine inhalation data, guinea pig gastric intubation data, and monkey IM data yield estimated ED_{50}/LD_{50}s of 0.80, 0.83, and 0.81, respectively. To derive these ratios, we assumed that effectivity and lethality PSs are equal within each species. We rejected the sublingual pigeon data. To avoid false precision, *AMedP-7.5* uses a ratio of 0.8, which means that $ED_{50} = 0.8 \times LD_{50} = 0.8 \times 28$ mg = 22.4 mg for the model. The assumed PS is 4.3 probits/log (dose).

Latent Period

After ingesting food contaminated with T-2, humans have experienced symptoms within half an hour.[1166] However, it is difficult to be sure whether these extremely rapid symptoms were due entirely to T-2 because foods contaminated with T-2 are also moldy, and deconvoluting the effects is problematic. The only known case of confirmed, acute exposure to T-2 in humans, without other potential sources of harm, is the lab workers who spilled a T-2 solution in their gloves and "experienced a burning sensation in their fingers about 4 hours post-exposure."[1167] Table 260 summarizes inhalation data from animal models that we considered in developing the latent period model.

Creasia and Lambert reported in 1987 that the exposure vehicle also plays a significant role in the rate of symptom onset. In rats and mice that received inhaled doses of LD_{50} or greater, death occurred in 1 to 2 hours if the T-2 had been suspended in saline; however, if the T-2 was dissolved in other solvents, even an "LD_{100}" dose did not produce death in less than 15 hours. While these data do not describe latent period explicitly, the

[1165] Wannemacher, Bunner, and Neufeld, "Toxicity of Trichothecenes," 522.
[1166] M. Peraica et al., "Toxic Effects of Mycotoxins in Humans," *Bulletin of the World Health Organization* 77, no. 9 (1999): 761 (Table 5).
[1167] Heubner et al., "Additional Toxins," 359.

significantly shorter time to death after T-2/saline is relevant. The same report also states that swine dosed with T- 2/ethanol exhibited symptoms in less than 4 hours.[1168]

Table 260. Latent Period after T-2 Aerosol Exposure in Animal Models

Source	Animal–Exposure Vehicle	Latent Period
Creasia and Lambert	Swine–Ethanol	Less than 4 hours
———	Rat or mouse–saline	(death within 1–2 hours)
———	Rat or mouse–not saline	(no death within 15 hours)
Pang et al.	Swine-Ethanol	3–4 hours
Creasia et al.. 1987	Young Adult Mice-Ethanol	Immediate to hours
———	Mice-Ethanol	Immediate to hours
Creasia et al., 1990	Rat-Ethanol	10 hours
Creasia and Thurman	Mice-Saline or ethanol	4–6 hours

Note: See Appendix B for full reference citations.

On the other hand, a 1993 study by Creasia and Thurman found no difference in the latent period for T-2/saline vs. T-2/ethanol. Mice exposed via inhalation to T-2 developed symptoms 4 to 6 hours after exposure, regardless of the exposure vehicle and regardless of whether they ultimately survived or died.[1169] Certainly, Creasia was aware of the conflict between his two reports, but he chose to publish the later data anyway. Since the 1993 data are more recent and are published in a peer-reviewed journal article rather than an internal USAMRIID report that is not publicly available, we did not use the 1987 Creasia and Lambert data from rats and mice for the latent period model.

The other inhalation literature includes swine that became ill in 3 to 4 hours,[1170] rats and guinea pigs that became lethargic 10 hours after exposure,[1171] and mice that were ill immediately after a 10 LD_{50} dose but were not ill for a few hours after a single LD_{50} dose.[1172] The single LD_{50} dose is more relevant for the present purpose. None of the other reports indicate a dose-dependent latent period, and the available data do not support the development of such a model.

Because nobody has reported latent period as a function of dose, it is important to be clear that the recommended value for the model is really a somewhat arbitrary choice

[1168] Creasia and Lambert, *Acute Respiratory Tract Toxicity*, 6, 13.
[1169] Creasia and Thurman, "Comparative Acute Inhalation Toxicity," 37.
[1170] Pang et al., "Experimental T-2 Toxicosis in Swine," 312. The pigs vomited 5 minutes after extubation, but this reaction may have been an aftereffect of the extubation itself or the anesthetic. The pigs did not show other signs of exposure until hours later.
[1171] Creasia et al., "Acute Inhalation Toxicity of T-2 Mycotoxin in the Rat and Guinea Pig," 56.
[1172] Creasia et al., "Acute Inhalation Toxicity of T-2 Mycotoxin in Mice," 231–232.

within the possible range. Considering the mice and swine data in Table 260 a value of 4 hours seems a reasonable choice for a constant value. This value is also the same latent period observed in the case of the lab workers who spilled a T-2 solution into their gloves.[1173] Four hours is on the conservative end of the range in Table 260. One final comment is that as long as the latent period is less than 1 day, different specific numbers of hours will not make a difference in the casualty estimate produced by *AMedP-7.5*, since it reports with 1-day time resolution.

Injury Profile

As noted previously, certain systemic symptoms occur regardless of the exposure route, but some symptoms are route specific. The Injury Profile only includes systemic and respiratory symptoms. *MMBC* provides the following succinct description, which is consistent with *MABW*:

> Upper respiratory exposure may result in nasal itching, pain, sneezing, epistaxis, and rhinorrhea. Pulmonary and tracheobronchial toxicity produces dyspnea, wheezing, and cough. Mouth and throat exposure causes pain and blood-tinged saliva and sputum. … Systemic toxicity can occur via any route of exposure, and results in weakness, prostration, dizziness, ataxia, and loss of coordination. Tachycardia, hypothermia, and hypotension follow in severe cases. Death may occur in minutes, hours, or days. The most common symptoms are vomiting, diarrhea, skin involvement with burning pain, redness and pruritus, rash or blisters, bleeding, and dyspnea. A late effect of systemic absorption is pancytopenia, predisposing to bleeding and sepsis.[1174]

This quotation appears to contradict the latent period model, but source of the quotation also states that "washing within 1 h may prevent toxicity entirely" and "washing contaminated skin with soap and water within 4 to 6 h removed 80-98% of the toxin, which prevented dermal lesions and death."[1175] Clearly, there is some uncertainty in the time to symptom onset. Since our purpose is to model the median response, the latent period model is not affected.

It is also important to note the following quotation:

> The early signs and symptoms of an aerosol exposure … would depend on particle size and toxin concentration. For a large-particle aerosol (particles > 10 μm, found in mist, fog, and dust …), the signs and symptoms would include rhinorrhea, sore throat, blurred vision, diarrhea, skin irritation (burning and itching), and dyspnea. Early (0–8h) signs and symptoms from

[1173] Heubner et al., "Additional Toxins," 359.
[1174] USAMRIID, *Medical Management of Biological Casualties*, 144.
[1175] Ibid., 141, 143.

> a deep-respiratory exposure (from aerosol particles in the 1- to 4-μm range) have not been fully evaluated but could include vomiting, diarrhea, skin irritation, and blurred vision.[1176]

Note that after stating that the signs and symptoms would differ for different particles sizes, the authors provide many of the same signs and symptoms for small and large particles. They also state that the later signs and symptoms "would probably be similar (except for the degree of skin rash and blisters) for both large-particle and deep-respiratory aerosol exposure."[1177] Thus, it seems the primary point is that there is considerable uncertainty about the effect of different sizes of particles.

Table 261 represents the T-2 Injury Profile in three stages, from the initial moderate symptoms mostly based on local effects (Stage 1), to severe and systemic effects (Stage 2), to sepsis and death (Stage 3). Note that survivors do not enter Stage 3 but will slowly recover from the Stage 2 symptoms.

Table 261. T-2 Mycotoxin Injury Profile

	Stage 1	Stage 2	Stage 3 (Nonsurvivors)
S/S	Dyspnea; wheezing; cough; sore throat; weakness; dizziness	Dyspnea; wheezing; cough; vomiting; bloody diarrhea; anorexia; abdominal pain; prostration; ataxia; gradual recovery in survivors	Tachycardia; progressive hypothermia; bloody diarrhea; hypotension; prostration; pancytopenia
S/S Severity	2 (Moderate)	3 (Severe)	4 (Very Severe)

Duration of Illness

Medical Aspects of Chemical and Biological Warfare states that at high doses in humans, "aerosolized trichothecenes may produce death within minutes to hours"[1178] and divides the signs and symptoms of respiratory exposure into early (0–8 hour) and late (8–24 hour) onset.[1179] No other source provides similar information, so Stage 2 for survivors and non-survivors will begin at 8 hours post exposure. The duration of Stage 1 is 8 hours. We chose the lowest end of the range to ensure a conservative estimate of the timing of casualties because of the poor quality of the data.

[1176] Wannemacher and Wiener, "Trichothecene Mycotoxins," 667.

[1177] Ibid.

[1178] Ibid., 658.

[1179] Ibid., 667. The authors note that the signs and symptoms have not been "fully evaluated." This caveat likely also applies to the timing.

For the duration of Stage 2 for survivors, there is one data point on human recovery after confirmed T-2 exposure. In the case of the laboratory workers who spilled a T-2 solution into their gloves, their severe cutaneous irritations had healed by Day 18 after exposure.[1180] Because no systemic symptoms occurred in the only human data available, we turned to animal models.

Several sources provide data, apparently on the same set of experiments, in which CMs survived after being given IM, IV, or cutaneous doses of T-2. The most direct comparison to the human data is that after cutaneous exposure, "Lesions were still evident 14 days after exposure but had almost completely resolved 28 days after."[1181] Other primate data show that after cutaneous liquid doses intended to be effective but not lethal, the primates seemed to recover over about 7 days, as indicated by their appetites, energy, and hematology.[1182] Note that changes in appetite, energy, and hematology relate to systemic effects rather than skin effects. Wannemacher, Bunner, and Neufeld state that the severity and duration of several symptoms appeared to be dose related but do not provide additional information that could be used to generate a dose-dependent model.[1183]

There are essentially two data points: recovery in about 14–18 days for one cutaneous dose (human) and recovery in 7 days for a lower cutaneous dose (NHP). How those doses relate to the LD_{50} or ED_{50} is unknown. Despite indications that duration and severity may be dose dependent, we have insufficient data to develop a dose-dependent model for the duration of Stage 2 in survivors. Thus, we use a constant-duration model, with a duration of 14 days as a compromise among the available data.

For non-survivors, animal models must inform the parameterization because no usable human data are available. Most animal models in inhalation experiments died within 1 day. Several reports explicitly state that the time to death was independent of dose. Monkeys given IM doses had mean time to death 18.4 hours,[1184] mice given IP or subcutaneous doses died between 15 and 25 hours,[1185] and rats given IP, oral, or

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[1180] J. R. Bamburg and F. M. Strong, "12,13-Epoxytrichothecenes," vol. VII of *Microbial Toxins*, ed. S. Kadis, A. Ciegler, and S. J. Ajl (New York, NY: Academic Press, 1971), 258.

[1181] Robert W. Wannemacher et al., "Dermal Toxicity of T-2 Toxin in Guinea Pigs, Rats, and Cynomolgus Monkeys," in *Trichothecenes and Other Mycotoxins*, ed. J. Lacey (Chichester, England: John Wiley & Sons Ltd., 1985), 428.

[1182] Bunner et al., "Pathophysiology of Acute T-2 Intoxication," 414.

[1183] Wannemacher, Bunner, and Neufeld, "Toxicity of Trichothecenes," 522.

[1184] Ibid. An unpublished report is cited as the original data source.

[1185] Ibid., 502. The following is cited as the original data source, but the article does not seem to contain the stated information: William L. Thompson and Robert W. Wannemacher, "Structure-Function Relationships of 12,13-Epoxytrichothecene Mycotoxins in Cell Culture: Comparison to Whole Animal Lethality," *Toxicon* 24, no. 10 (1986): 985–994.

inhalational doses died between 9 and 18 hours.[1186] No reports claimed that the time to death is dose dependent. Other reports that do not specifically discuss dose dependence but whose data do not demonstrate such dependence include the following: intragastrically dosed guinea pigs died between 6 and 24 hours;[1187] IV-dosed pigs died as soon as 8 to 10 hours;[1188] IM-dosed rats, guinea pigs, and CMs had mean times of death between 14 and 19 hours;[1189] rats that inhaled a lethal dose died within 12 hours;[1190] and rats given lethal intratracheal doses died between 12 and 24 hours after dosing.[1191]

Assuming these data extrapolate to human inhalation cases, the time to death could feasibly be anywhere between 8 hours post exposure (beginning of Stage 2) and 24 hours, but it is not possible to model the duration of illness with a probability distribution. Because several reports indicated the time to death is not dependent on dose and no other reports contradict, the recommended model is a constant time until death. To attempt to represent the median individual, given the bounds of 8 and 24 hours, the time to death is 16 hours. Because no data are available to dictate otherwise, we assume that the time spent in Stage 2 and Stage 3 is split evenly in the time remaining after the end of Stage 1 (4 hours in each of Stages 2 and 3). If supporting data become available, a probabilistic, dose-independent model for the entire duration of illness would be preferred.

A final comment is that since the total duration of illness in non-survivors is less than 1 day, the specific number of hours does not matter because of *AMedP-7.5*'s time resolution of 1 day for output reporting.

Medical Countermeasures and Treatment Model

"No specific therapy for trichothecene-induced mycotoxicosis is known." Symptomatic care for T-2 mycotoxicosis varies widely depending on the specific symptoms exhibited. For ocular exposure, eyes should be irrigated, and the casualty needs detailed ophthalmologic evaluation. Skin symptoms can be treated with lotions and creams. Respiratory symptoms, such as sore throat and cough, can be treated with steam inhalation

[1186] Wannemacher, Bunner, and Neufeld, "Toxicity of Trichothecenes," 506. Personal communication and the following abstract are cited as the data source: Creasia et al., "Acute Inhalation Toxicity of T-2 Toxin in the Rat and Mouse."
[1187] DeNicola et al., "T-2 Toxin Mycotoxicosis," 602; Marrs et al., "Acute Toxicity of T2 Mycotoxin," 261; Creasia et al., "Acute Inhalation Toxicity of T-2 Mycotoxin in the Rat and Guinea Pig," 56.
[1188] Pang et al., "Experimental T-2 Toxicosis in Swine," 309.
[1189] Wannemacher et al., "Dermal Toxicity of T-2 Toxin," Table 2.
[1190] Creasia et al., "Acute Inhalation Toxicity of T-2 Mycotoxin in the Rat and Guinea Pig," 56.
[1191] Fairhurst et al., "Acute Toxicity of T2 Toxin," 37.

and cough suppressants. If pulmonary edema occurs, it should be treated by standard methods.[1192]

Because no data are available on medical treatment of humans exposed to T-2, we have no basis on which to recommend modified parameters; there is no treated model.

Model Summary

Table 262 and Table 263 summarize the model parameters for T-2 mycotoxicosis used in *AMedP-7.5*. While the parameters in the tables below represent current best estimates, any new data that become available, particularly for acute inhalational exposure in humans or nonhuman primates, would significantly improve the model.

Table 262. T-2 Mycotoxin Model Parameters Summary Table

Submodel	Type	Parameters
Effectivity	Lognormal distribution	ED_{50} = 22.4 mg Probit slope = 4.3 probits/log (dose)
Lethality	Lognormal distribution	LD_{50} = 28 mg Probit slope = 4.3 probits/log (dose)
Latent Period	Constant	4 hours
Duration of Illness		
Stage 1 (all)	Constant	8 hours
Stage 2 (survivors)	Constant	14 days
Stage 2 (non-survivors)	Constant	4 hours
Stage 3 (non-survivors)	Constant	4 hours

Table 263. T-2 Mycotoxin Injury Profile

	Stage 1	Stage 2	Stage 3 (non-survivors)
Signs and Symptoms (S/S)	Dyspnea; wheezing; cough; sore throat; weakness; dizziness	Dyspnea; wheezing; cough; vomiting; bloody diarrhea; anorexia; abdominal pain; prostration; ataxia; gradual recovery in survivors	Tachycardia; progressive hypothermia; bloody diarrhea; hypotension; prostration; pancytopenia
S/S Severity	2 (Moderate)	3 (Severe)	4 (Very Severe)

Cohorts and Special Considerations (*AMedP-7.5 Section 5.2.17.3*)

Cohort populations are calculated according to the standard equations for E, F, and S in *AMedP-7.5* and then split based on dose ranges; no further explanation is warranted.

[1192] The information in this paragraph all comes from Heubner et al., “Additional Toxins,” 364.

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1.34. Ebola Virus Disease Information (*AMedP-7.5 Section 5.2.18*)

This chapter is intentionally very short—it gives the basis for the numbers included in *AMedP-7.5*, but is not an attempt at a thorough literature review for Ebola Virus Disease. As stated in *AMedP-7.5*:

> Although it is recognized that Ebola virus is important, as an outbreak of Ebola Virus Disease (EVD) could cause a significant number of casualties, the West African Ebola virus epidemic has shown that previously developed human response models for EVD do not accurately reflect the propagation of disease within a population. Further, at the time this document was prepared, characterization of the West African Ebola virus epidemic in the scientific literature was partial at best. Until more information on the West African Ebola virus epidemic is published, confidence in the accuracy of any new EVD model will be low.
>
> However, recognizing that in some situations, even outdated information may be better than no information at all, Section 5.2.18 contains approximations of parameter values for EVD, based largely on models that were developed *before* the West African Ebola virus epidemic and some limited new information from the West African Ebola virus epidemic. However, note that the information in Section 5.2.18 is intentionally presented in a format that *cannot* be easily used in the biological agent human response frameworks presented in this document.[1193]

[1193] NATO, *AMedP-7.5*, 1-5.

The aerosol infectivity estimate is based on evidence from aerosol challenge NHP experiments[1194] and SME agreement as reported in a previous IDA analysis.[1195]

The range of CFRs given is based on analysis conducted for the previous IDA analysis, which reported the CFR for 24 outbreaks that occurred between 1976 and 2012.[1196] We also note that the CFR is dependent on strain and the quality of medical care provided. Information provided on the incubation period and duration of illness—which may also be dependent on the strain—are based on the IDA analysis and three other sources.[1197]

[1194] The following five sources have shown that by aerosol challenge with varying strains of Ebola virus, various types of NHP become infected with doses even as low as single-digit PFUs: E. Johnson, N.Jaax, J. White, and P. Jahrling, "Lethal Experimental Infections of Rhesus Monkeys by Aerosolized Ebola Virus," *International Journal of Experimental Pathology* 76 (1995): 227–236; D. A. Alves et.al., "Aerosol Exposure to the Angola Strain of Marburg Virus Causes Lethal Viral Hemorrhagic Fever in Cynomolgus Macaques," *Veterinary Pathology* 47, no. 5 (2010): 831–851; William D. Pratt et al., "Protection of Nonhuman Primates against Two Species of Ebola Virus Infection with a Single Complex Adenovirus Vector," *Clinical and Vaccine Immunology* 17, no. 4 (2010): 572–581; Douglas S. Reed et al., "Aerosol exposure to Zaire ebolavirus in three nonhuman primate species: differences in disease course and clinical pathology," *Microbes and Infection* 13, no. 11 (2011): 930–936; and Elizabeth E. Zumbrun et al., "A Characterization of Aerosolized Sudan Virus Infection in African Green Monkeys, Cynomolgus Macaques, and Rhesus Macaques," *Viruses* 4 (2012): 2115–2136.

[1195] Deena S. Disraelly et al., *Estimated Therapeutic Troop Equivalent Doses for Ebola and Marburg Hemorrhagic Fevers*, IDA Document NS D-4851 (Alexandria, VA: IDA, March 2013), 24–25.

[1196] Disraelly et al., *Estimated Therapeutic Troop Equivalent Doses*, Table 7.

[1197] Martin Eichner, Scott F. Dowell, and Nina Firese, "Incubation Period of Ebola Hemorrhagic Virus Subtype Zaire," *Osong Public Health and Research Perspectives* 2, No. 1 (2001): 3–7; WHO Ebola Response Team, "Ebola Virus Disease in West Africa — The First 9 Months of the Epidemic and Forward Projections," *The New England Journal of Medicine* 371, No. 16 (2014): 1481–1495; and John M. Drake et al., "Transmission Models of Historical Ebola Outbreaks," *Emerging Infectious Disease* 21, No. 8 (2015): 1447–1450.

1.35. Recommendations for *AMedP-7.5*(*B*)

The following is a list of items that should be addressed in the development of *AMedP-7.5*(*B*). We are not sure there are enough data to implement all the recommendations; the first step should be a feasibility study for each item. Enlisting the help of SMEs may be warranted.

- Add percutaneous liquid models for GA, GD, and GF.
- Add percutaneous vapor model for VX.
- If, as a commenter suggested, the severe percutaneous liquid VX toxicity parameters have been retracted (need evidence from a published document), consider removing the Severe Injury Profile for percutaneous liquid VX.
- Consider different Injury Profiles for the different nerve agents (in particular, timing should probably differ).
- A new contagious disease model framework with the following features:
  - No reliance on the epidemiology of historical outbreaks for its predictions.
  - Ability to track the time individuals have spent in each stage of illness (or cohort within the model).
  - Designed from the ground up to include the effects of medical treatment, isolation, and quarantine.
  - Uses full distributions (means and standard deviations) for incubation period and duration of illness.
- Add a functional Ebola model that works with the new contagious disease model framework.
- Include uncertainty estimates for the all parameters (toxicities, biological agent submodels, etc.), and include the mathematics and algorithm for generating overall uncertainty estimates for the output tables.

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Illustrations

Figures

Tables

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Glossary, Acronyms, and Symbols

Glossary

See Chapter 2, section B. Additional definitions are below.

Median infectious dose. Dose resulting in infection and illness for 50% of the exposed population.

Median lethal dose. Dose resulting in lethality for 50% of the exposed population.

Acronyms and Symbols

%BSA Percentage body surface area burned to second- or third-degree level

AAP Allied Administration Publication
AC Hydrogen cyanide
ACH Air changes per hour
ADMP Active duty military personnel
AEGL Acute Exposure Guideline Level
AGM African green monkey
AJP Allied Joint Publication
AMA American Medical Association
AMedP Allied Medical Publication
APF Aggregate Protection Factor
ARS Acute radiation syndrome
AT&D Atmospheric transport and dispersion
ATSDR Agency for Toxic Substances and Disease Registry
AVA Anthrax Vaccine Adsorbed

BAL Bronchoalveolar lavage fluid
BD Burdening doese
BDO Battle dress overgarment
BDU Battle dress uniform
BSA Body surface area

CAT Casualty category
CBRN Chemical, biological, radiological, and nuclear
CDC Centers for Disease Control and Prevention
CDF Cumulative distribution function
CER Case encephalitis rate
CFR conditional probability of death given illness or the fraction of ill individuals that die (18-3)
CFU Colony forming unit

CG Phosgene
CI Confidence interval
CK Cyanogen chloride
Cl_2 Chlorine
CM Cynomolgus macaque
CNS Central nervous system
ColPro Collective protection
CONV Convalescent
CRN Chemical, radiological, and nuclear
CSAC Chemical Security Analysis Center
Ct Concentration time
CV Cerebrovascular

DIA Defense Intelligence Agency
DICE DNA Improved Casualty Estimation
DNA Defense Nuclear Agency
DOD U.S. Department of Defense
DOW Died of wounds
DRF Dose reduction factor
DTRA Defense Threat Reduction Agency

ECBC Edgewood Chemical Biological Center
ECt_{50} Effective median dosage (concentration time)
ED_{50} Median effective dose
EEE Eastern equine encephalitis
EEEV Eastern equine encephalitis virus
EPA Environmental Protection Agency
EPD Equivalent prompt dosage
EVD Ebola Virus Disease

FDA U.S. Food and Drug Administration
FIA Free-in-air
GA Tabun
GB Sarin
G-CSF Granulocyte-colony stimulating factor
GD Soman
GF Cyclosarin
GI Gastrointestinal
$GPID_{50}$ Guinea pig intraperitoneal ID_{50}s
Gy Gray

H_2S Hydrogen sulfide
HCl Hydrochloric acid
HD Distilled mustard

HEPA High efficiency particulate air
HP Hematopoietic
HPAC Hazard Prediction and Assessment Capability
hr Hour

ICU Intensive care unit
ID Intradermal
ID_{50} Median infectious dose
IDA Institute for Defense Analyses
IDP Intermediate Dose Program
IgM Immunoglobulin M
IM Intramuscular
IN Intranasal
IND Investigational new drug
IP Intraperitoneal
IPE Individual protective equipment
IV Intravenous

J/cm^2 Joule per square centimeter

KAMI Knowledge Acquisition Matrix Instrument
kg Kilogram
KIA Killed in action
kJ/m^2 Kilojoule per square meter
kPa Kilopascal

LD_{50} Median lethal dose
LVS Live vaccine strain

m Meter
MABW *Medical Aspects of Biological Warfare*
MEG Military Exposure Guidelines
mg Milligram
Milirary research volunteer
min Minute
$MIPLD_{50}$ Mouse intraperitoneal median lethal doses
MLE Maximum likelihood estimation
MMAD Mass median aerodynamic diameter
MMBC *Medical Management of Biological Casualties Handbook*
MRV Medical research volunteer
MTF Medical treatment facility
MTOR Medical treatment outcome reporting

N.O.I. No observable injury

N/A Not applicable
NA North American
NATO North Atlantic Treaty Organization
NBC Nuclear, biological, and chemical
NHP Non-human primate

OP Organophosphorus

PAR Population at risk
PDF Probability density function
PDT Probability Density Table
PFU Plaque forming units
PMN Polymorphonuclear leukocytes
ppm Parts per million
PRCC *Personnel Risk and Casualty Criteria for Nuclear Weapons Effects*
PS Probit slope
PS Probit slope
PSR Pacific Sierra Research Corporation

RBE Relative biological effectiveness
RDD Radiological dispersal device
RIP Ribosome-inactivating protein
RIPD Radiation-Induced Performance Decrement [software]
RM Rhesus macaque
RTD Return to Duty

S/S Signs and symptoms
SA South American
SEB Staphylococcal enterotoxin B
SEIRP Susceptible, Exposed and infected, Infectious, Removed, and Prophylaxis efficacious
SME Subject-matter expert
STANAG NATO standardization agreement

TBq Terabecquerel (10^{12} becquerels)
TIC Tox industrial compound
TLE Toxic load equivalent
TLM Toxic load modeling
TRM Technical Reference Manual
TSS Toxic shock syndrome

USAMRICD U.S. Army Medical Research Institute of Chemical Defense
USAMRIID U.S. Army Medical Research Institute of Infectious Diseases

VBIED Vehicle-borne improvised explosive device
VEE Venezuelan equine encephalitis
VEEV Venezuelan equine encephalitis virus
VX O-Ethyl-S-(2-diisopropylaminoethyl) methyl phosphonothiolate

WEEV Western equine encephalitis virus
WHO World Health Organization
WIA Wounded in action
WIA(1^+) Wounded in action (Severity Level 1 (“Mild”) or greater)
WIA(2^+) Wounded in action (Severity Level 2 (“Moderate”) or greater)
WIA(3^+) Wounded in action (Severity Level 3 (“Severe”) or greater)

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This Technical Reference Manual (TRM) serves as a supplement to *Allied Medical Publication 7.5* (*AMedP-7.5*), documenting the analyses, rationale, and underlying data utilized in the development of the methodology. This document provides information beyond the scope of *AMedP-7.5* that will allow for transparency and verification of the methodology.

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