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Evaluation of Military Field-Water Quality

Volume 4. Health Criteria and Recommendations for Standards
Part 2. Interim Standards for Selected Threat Agents and Risks from Exceeding These Standards

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The purpose of this report is to develop drinking-water standards for field water for selected threat agents of concern, including radioactivity. The threat agents of concern in addition to radioactivity are the classical chemical-warfare (CW) compounds hydrogen cyanide, organophosphorus nerve agents (i.e., GA, GB, GD, and VX), and lewisite (an arsenical vesicant), as well as a fungal metabolite identified only recently as a possible threat agent, the trichothecene mycotoxin, T-2. All of these substances are of concern because they could appear in water and they can be responsible for degrading performance due to their toxic properties. The recommended standards are applicable only to military personnel deployed in the field, and they are meant to protect against performance-degrading effects resulting from the ingestion of the substances in field water consumed at rates of up to 5 and 15 L/d for a period lasting up to 7 d. However, due to the nature of radioactivity and because radioactive material could be dispersed over a very wide geographic area following a military exchange
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with nuclear weapons, standards are also recommended for up to 1-y exposure in a radioactive environment. Additionally, the standards recommended for all the threat agents, except hydrogen cyanide, are interim ones because (1) in the case of radioactivity, it may not be possible to dismiss exposure via pathways other than ingestion of field water because of the special properties of radioactivity, and (2) for the other compounds, the data are from limited studies with human volunteers and laboratory animals. The standards recommended for hydrogen cyanide are not assigned an interim status because there is no reason to believe that the standards recommended for cyanide in field water in the first part of this volume (see Chapter 8 in Volume 4, Part 1) cannot be applied to the threat agent hydrogen cyanide and also because the data from which the standards for cyanide were developed are not quite so limited.

This report is part two of the fourth volume of a nine-volume study entitled Evaluation of Military Field-Water Quality. Titles of the other volumes are as follows: Vol. 1, Executive Summary; Vol. 2, Constituents of Military Concern from Natural and Anthropogenic Sources; Vol. 3, Opportunity Poisons; Vol. 4 (Part 1), Health Criteria and Recommendations for Standards: Chemicals and Properties of Military Concern Associated with Natural and Anthropogenic Sources; Vol. 5, Infectious Organisms of Military Concern Associated with Consumption: Assessment of Health Risks, and Recommendations for Establishing Related Standards; Vol. 6, Infectious Organisms of Military Concern Associated with Nonconsumptive Exposure: Assessment of Health Risks, and Recommendations for Establishing Related Standards; Vol. 7, Performance Evaluation of the 600-GPH Reverse Osmosis Water Purification Unit (ROWPU): Reverse Osmosis (RO) Components; Vol. 8, Performance of Mobile Water Purification Unit (MWPU) and Pretreatment Components of the 600-GPH Reverse Osmosis Water Purification Unit (ROWPU) and Consideration of Reverse Osmosis (RO) Bypass, Potable-water Disinfection, and Water-Quality Analysis Techniques; and Vol. 9, Data for Assessing Health Risks in Potential Theaters of Operation for U.S. Military Forces.

FOREWORD

This report is part two of the fourth volume of a nine-volume study entitled Evaluation of Military Field-Water Quality. Titles of the other volumes are as follows: Vol. 1, Executive Summary; Vol. 2, Constituents of Military Concern from Natural and Anthropogenic Sources; Vol. 3, Opportunity Poisons; Vol. 4 (Part 1), Health Criteria and Recommendations for Standards: Chemicals and Properties of Military Concern Associated with Natural and Anthropogenic Sources; Vol. 5, Infectious Organisms of Military Concern Associated with Consumption: Assessment of Health Risks, and Recommendations for Establishing Related Standards; Vol. 6, Infectious Organisms of Military Concern Associated with Nonconsumptive Exposure: Assessment of Health Risks, and Recommendations for Establishing Related Standards; Vol. 7, Performance Evaluation of the 600-GPH Reverse Osmosis Water Purification Unit (ROWPU): Reverse Osmosis (RO) Components; Vol. 8, Performance of Mobile Water Purification Unit (MWPU) and Pretreatment Components of the 600-GPH Reverse Osmosis Water Purification Unit (ROWPU) and Consideration of Reverse Osmosis (RO) Bypass, Potable-Water Disinfection, and Water-Quality Analysis Techniques; and Vol. 9, Data for Assessing Health Risks in Potential Theaters of Operation for U.S. Military Forces.

The nine volumes of this study contain a comprehensive assessment of the chemical, radiological, and biological constituents of field-water supplies that could pose health risks to military personnel as well as a detailed evaluation of the field-water-treatment capability of the U.S. Armed Forces. The scientific expertise for performing the analyses in this study came from the University of California Lawrence Livermore National Laboratory (LLNL) in Livermore, CA; the University of California campuses located in Berkeley (UCB) and Davis (UCD), CA; the University of Illinois campus in Champaign-Urbana, IL; and the consulting firms of IWG Corporation in San Diego, CA, and V.J. Ciccone & Associates (VJCA), Inc., in Woodbridge, VA. Additionally a Department of Defense (DoD) Multiservice Steering Group (MSG), consisting of both military and civilian representatives from the Armed Forces of the United States (Army, Navy, Air Force, and Marines), as well as representatives from the U.S. Department of Defense, and the U.S. Environmental Protection Agency provided guidance, and critical reviews to the researchers. The reports addressing chemical, radiological, and biological constituents of field-water supplies were also reviewed by scientists at Oak Ridge National Laboratory in Oak Ridge, TN, at the request of the U.S. Army. Furthermore, personnel at several research laboratories, military installations, and agencies of the U.S. Army and the other Armed Forces provided technical assistance and information to the researchers on topics related to field water and the U.S. military community.

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PREFACE

This is the fourth volume of the nine volume report, Evaluation of Military Field-Water Quality, and it contains the health criteria and recommendations for standards for the constituents and properties of field water identified as being of military concern. Because of the nature and the amount of supporting information accompanying these recommendations, the volume has been divided into two parts. Part 2 addresses criteria and recommendations for interim standards for selected threat agents of concern, including radioactivity, and the risks from exceeding these standards. These substances typically will be of military origin, and therefore they are considered to be relevant as field-water contaminants only during military conflicts. The threat agents of concern were identified by U.S. military and civilian members of the Department of Defense (DoD) Multiservice Steering Group (MSG), a committee established for the specific purpose of guiding and reviewing the research effort on the Evaluation of Military Field-Water Quality. The field-water constituents and properties that are associated with natural or anthropogenic sources are presented in Part 1 of this volume. These properties and substances were identified in screening analyses contained in Part 1 (Organic Chemicals), Part 2 (Pesticides), and Part 3 (Inorganic Chemicals and Physical Properties) of Volume 2 (Constituents of Military Concern from Natural and Anthropogenic Sources).

EVALUATION OF MILITARY FIELD-WATER QUALITY
VOLUME 4. HEALTH CRITERIA AND RECOMMENDATIONS FOR STANDARDS

Part 2. Interim Standards for Selected Threat Agents and Risks from Exceeding These Standards

ABSTRACT

The purpose of this report is to develop drinking-water standards for field water for selected threat agents of concern, including radioactivity. The threat agents of concern in addition to radioactivity are the classical chemical-warfare (CW) compounds hydrogen cyanide, organophosphorus nerve agents (i.e., GA, GB, GD, and VX), and lewisite (an arsenical vesicant), as well as a fungal metabolite identified only recently as a possible threat agent, the trichothecene mycotoxin T-2. All of these substances have been identified as being of possible concern because they could appear in water and they can be responsible for degrading performance due to their toxic properties. The recommended standards are applicable only to military personnel deployed in the field, and they are meant to protect against performance-degrading effects resulting from the ingestion of the substances in field water consumed at rates of up to 5 and 15 L/d for a period lasting up to 7 d. However, due to the nature of radioactivity and because radioactive material could be dispersed over a very wide geographic area following a military exchange with nuclear weapons, standards are also recommended for up to 1-y exposure in a radioactive environment. No additional research on radioactivity is recommended. Additionally, the standards recommended for all the threat agents, except hydrogen cyanide, are interim ones because (1) in the case of radioactivity it may not be possible to dismiss exposure via pathways other than ingestion of field water because of the special properties of radioactivity, and (2) for the other compounds, the data are from limited studies with human volunteers and laboratory animals. The standards recommended for hydrogen cyanide should not be assigned an interim status because there is no reason to believe that the standards recommended for cyanide in field water in the first part of this volume (see Chapter 8 in Volume 4, Part 1) cannot be applied to the threat agent hydrogen cyanide and also because the data from which the standards for cyanide were developed are not quite so limited. The standards recommended for drinking water consumption rates of 5 and 15 L/d are provided in Table I, following.

Table I. Summary of recommended field-water-quality standards for selected threat agents of concern, including radioactivity, for ingestion up to 7 d, and similar standards that are currently applicable. A long-term standard (≤1 y) for radioactivity is also provided.[a]

	Recommended standards		TB MED 229	TB MED 577	QSTAG 245
Constituent	5 L/d	15 L/d	5 L/d	5 L/d	5 L/d
Hydrogen cyanide (mg/L)	6	2	20	20	20
Radioactivity[a] (μCi/L)					
Short-term:			_[b]	_[b]	_[b]
Gross alpha and/or gross beta	8	3			
Specified[c]	ALI/35	ALI/105			
Long-term:					0.06[d]
Gross alpha and/or gross beta	0.1	0.05			
Specified[c]	ALI/1825	ALI/5475			
OP threat agents (μg/L)[e]	12	4	20	20	20
T-2 toxin (μg/L)	26	8.7			
Lewisite: arsenic fraction (mg/L)	0.08	0.027	2	2	2

[a]Long-term (≤1 y) as well as short-term (≤7 d) standards were developed because of the nature of radioactivity and the possibility that radioactive material could be dispersed over a very wide geographic area following a military exchange with nuclear weapons.

[b]If external radiation permits military personnel to occupy a location, then water is considered suitable for consumption for a period lasting up to 7 d.

[c]If specific radionuclides are known to be present, then the annual limit on intake (ALI) should be divided by the stated factors.

[d]A long-term standard (≤1 y) for mixed fission products.

[e]If pretreatment with pyridostigmine bromide is enforced, the recommended concentrations are 4.7 and 1.6 μg/L for 5 and 15 L/d consumption rates.

CHAPTER 1. INTRODUCTION

J. I. Daniels* and D. W. Layton*

FIELD-WATER-QUALITY STANDARDS FOR SELECTED THREAT AGENTS: BACKGROUND

Threat agents typically include the nuclear and chemical-warfare munitions in military arsenals. These munitions generally are designed to be used overtly and directly on opposing military forces to produce lethality and incapacitation. For this reason, threat agents are considered to be relevant as possible contaminants of field-water supplies used as sources of drinking water for military personnel only during military conflicts in which nuclear or chemical attack is anticipated.

As a consequence of known threat capabilities, the threat agents that could appear in field water under the previously mentioned circumstances, and the ones that are of particular concern are radioactivity; the classical chemical-warfare compounds hydrogen cyanide, organophosphorus (OP) nerve agents (i.e., GA, GB, GD, and VX), lewisite (i.e., an arsenical vesicant); and a fungal metabolite identified only recently as a possible threat agent, the trichothecene mycotoxin T-2. Although drinking-water standards for field-water supplies for all the threat agents just mentioned, except T-2 toxin, presently exist (see U.S. Army Technical Bulletins TB MED 229[1] and TB MED 577[2]), comprehensive review and revision of these standards has not been performed since the 1960's. Accordingly, this part of Volume 4 is devoted to (1) reviewing and assessing the potential health effects associated with ingestion of each of the threat agents of concern; (2) defining applicable criteria for establishing revised drinking-water standards for each of these threat agents in field water; (3) recommending revision to the current field-water-quality standards for each of the threat agents; and (4) assessing the health risks that might result if the recommended standards for a threat agent are exceeded. Hydrogen cyanide is not addressed in detail in this part of Volume 4 because recommendations for field-water-quality standards for cyanide from industrial wastewater discharge were addressed in the first part of this volume (see Chapter 8 in Volume 4, Part 1[3]), the health risks that could result if these recommended standards for cyanide are exceeded are presented in Volume 9,[4] and there is no evidence to indicate

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that such standards and health risks for cyanide should not be applied to the threat agent hydrogen cyanide in field water.

As will be discussed later in this chapter, the recommended standards for the threat agents of concern are applicable only to military personnel deployed in the field, and they are meant to protect against performance-degrading effects resulting from the ingestion of these substances in field water consumed at rates of up to 5 and 15 L/d for a period lasting up to 7 d. However, due to the nature of radioactivity and because radioactive material could be dispersed over a very wide geographic area following a military exchange with nuclear weapons, standards are also recommended for radioactivity for an exposure lasting up to 1 y.

The recommended field-water-quality standards for each of the threat agents except hydrogen cyanide, discussed in this volume are labeled "interim" because (1) in the case of radioactivity, it may not be possible to dismiss exposure via pathways other than ingestion of field water because of the special properties of radioactivity, and (2) for the other threat agent compounds of concern, the data are from limited studies with human volunteers and laboratory animals. The recommended standards for hydrogen cyanide are not assigned an interim status because there is greater confidence in the data from which the recommended field-water-quality standards for cyanide were developed (see Chapter 8 in Volume 4, Part 1[3]). The last chapter of this volume suggests research for improving the confidence in the data from which interim standards were developed.

GENERAL PURPOSE OF DRINKING-WATER STANDARDS

Drinking-water standards for field water are necessary to prevent performance-degrading effects involving (1) physical abilities associated with operative sensory, neuromuscular, cardiovascular, respiratory, gastrointestinal, and cutaneous systems; (2) mental faculties related to properly functioning cognitive processes needed for reasoning and decision making; and (3) behavioral attributes involving control of emotions, discipline, motivation, morale, and cooperation. The basic purpose of field-water-quality standards is to prevent water from becoming a source of casualties or causing decrements in the performance of military populations with battlefield responsibilities. The field-water-quality standards that are recommended for the threat agents of concern are intended to protect essentially all military occupational specialties, from infantryman to fighter pilot. The recommended standards are definitely not

applicable to populations of civilians and do not represent water-quality standards for drinking-water treated at properly functioning fixed installations.

To develop the standards for the threat agents of concern in a consistent fashion, we relied on a set of assumptions and definitions regarding the population at risk, exposure scenarios, etc. In the discussion below, the rationale and basis of the key considerations affecting the analyses supporting the recommended standards are described.

WATER CONSUMPTION RATES AND EXPOSURE PERIODS

Maximum water consumption rates for military personnel appear in the Water Consumption Planning Factors Study[5] prepared in 1983 by the Directorate of Combat Developments and also in Chapter 3 of the 1983 Edition of the U.S. Army's Commander's Handbook for Water Usage in Desert Operations, Field Manual No. 10-52-1.[6] These documents indicate that the maximum individual daily amount of drinking water required by military personnel in order to remain combat effective can range from about 5 to 15 L/d, depending on climate, season, intensity of work, and type of battlefield (i.e., conventional, in which nuclear and/or chemical attack, in particular, are not anticipated; or integrated, in which nuclear and/or chemical attack are anticipated). Accordingly, the 5 and 15 L/d maxima are used for developing recommendations for field-water-quality standards in this volume. The use of these values for standards development was supported by the Department of Defense (DoD) Multiservice Steering Group (MSG), a committee established for the specific purpose of guiding and reviewing the research effort on this multivolume series, Evaluation of Military Field-Water Quality. Such daily maximum consumption rates are also consistent with the operational experiences of the Israeli Defense Forces and observations by U.S. Army Medical Services Officers at training exercises for National Guard armor battalions in the Mojave Desert of California.[7]

Another important consideration in developing field-water-quality standards was the duration over which consumption of field water would take place. According to the 1986 edition of U.S. Army Technical Bulletin No. TB MED 577, titled Occupational and Environmental Health Sanitary Control and Surveillance of Field Water Supplies,[2] consumptive use of field water is divided into two scenarios: short-term consumption lasting up to seven consecutive days (i.e., $\leq$ 7 d) and long-term consumption lasting up to one year but exceeding seven days (i.e., $\leq$ 1 y but $>$ 7 d). In the opinion of the military and civilian experts on the DoD MSG, military personnel are not expected to be in a threat agent environment, at least one created by the use of a chemical-warfare munition, for longer than a relatively short period of time, defined to be less than or equal to 7 d. Yet,

military personnel could be in a radioactive environment for a period lasting more than 7 d and perhaps as long as 1 y, because of the nature of radioactivity and the possibility of wider dispersion of fallout from nuclear weapons than from chemical-warfare munitions. For these reasons, short-term drinking-water standards that are applicable to consumption of field water for a period not exceeding 7 d are recommended for all the threat agents, including radioactivity, and long-term drinking-water standards applicable to consumption of field water for a period lasting up to 1 y are recommended for radioactivity.

OTHER CONSIDERATIONS

The paramount focus of the research presented in this report is to develop and recommend standards that will prevent field-water-related casualties and performance degradation in those military populations deployed in field-combat situations. Consequently, neither the existence nor performance of water-quality monitoring devices nor the efficiency of water-purification equipment were a consideration in the development of the field-water-quality standards that are recommended. Similarly, recommended standards do not protect against health effects such as carcinogenesis or teratogenesis.

When possible, human toxicological data with respect to ingestion were evaluated for ascertaining dose-response relationships. If such human data were limited, inadequate, or absent, toxicity data for animals were evaluated. The health consequences of synergistic interactions between the constituents of military concern could not be assessed because relevant data were not available in the literature.

OBJECTIVES OF THE FIELD-WATER-QUALITY STANDARDS

The specific objectives of the short-term field-water-quality standards were defined by the DoD MSG. These objectives are the cornerstone upon which the recommendations for field-water-quality standards are based. Specifically, short-term standards should protect against any health-effect end point that can adversely impact the capability of an individual to conduct a military mission (i.e., prevent operational degradation). However, as stated in TB MED 577,[2] a field commander forced to institute short-term standards must acknowledge the potential for reduced combat efficiency each day that short-term standards remain in effect; the risk of morbidity from prolonged exposure to field water meeting short-term standards is especially great for threat agents, which are toxic. Alternatively, long-term standards, which are developed only for radioactivity, should

protect against any adverse health effects that could appear during a 1-y period of exposure.

Neither the short-term field-water-quality standards recommended for all the threat agents nor the long-term standards recommended only for radioactivity address adverse health effects such as carcinogenesis, teratogenesis, or latent or chronic effects that in combat situations typically are not as imminent or consequential as a performance degradation induced by acute health effects. Nevertheless, potential chronic effects are identified in discussions accompanying the recomendations for standards if such information is available in the literature.

CHARACTERISTICS OF THE POPULATION AT RISK

The military populations at risk are those deployed in the field and composed predominantly of male adults who are between 18 and 55 years old, weigh an average 70 kg (approximately 154 lb), and are in good health. The possibility that female adults will not be excluded from battlefield responsibilities, particularly those of a supporting nature, was also considered. The female military populations would be between 18 and 55 years old and in good health, but they would weigh an average 60 kg (132 lb). The military populations of interest are also regarded to be (1) adequately immunized; (2) satisfactorily nourished (such that any nutritional deficiency or salt imbalance is not significant); and (3) without physical or mental problems that could impair the physical abilities, mental faculties, or behavioral attributes required for performing assigned tasks in a combat situation. Finally, due to the nature of battlefield situations and requirements, military personnel typically will not be acclimated to the field water in a specific geographic region prior to arrival.

RECOMMENDATIONS FOR FIELD-WATER-QUALITY STANDARDS

The field-water-quality standards recommended in this volume are presented in Table 1. Table 1 also contains comparable standards for drinking water published in the last (i.e., 1975) edition of U.S. Army Technical Bulletin No. TB MED 229,[1] the 1986 edition of U.S. Army Technical Bulletin No. TB MED 577,[2] and the most recent version of Quadripartite Standardization Agreement (QSTAG) 245.[8]

As discussed earlier, the recommended field-water-quality standards presented in Table 1 were not developed on the basis of detection capabilities available to military

forces nor on the treatment efficiency attainable by military water-purification equipment. The methodologies used to develop the recommended field-water-quality standards were not the same for all the constituents of field water identified to be of concern. Nevertheless, the recommended standards were developed to be consistent with each other. Each standard provides protection against performance-degrading effects in military personnel, and is applicable to all military occupational specialties. The standards recommended do not address health effects such as carcinogenesis or teratogenesis.

Table 1. Recommended field-water-quality standards for selected threat agents of concern, including radioactivity, for ingestion up to 7 d, and similar standards that are currently applicable. A long-term standard (≤1 y) for radioactivity also is provided.[a]

	Recommended standards[b]		TB MED 229[c]	TB MED 577[d]	QSTAG 245[e]
Constituent	5 L/d	15 L/d	5 L/d	5 L/d	5 L/d
Hydrogen cyanide (mg/L)	6[f]	2[f]	20	20	20
Radioactivity[a] (μCi/L)					
Short-term:			–[g]	–[g]	–[g]
Gross alpha and/or gross beta	8	3			
Specified	ALI/35[h]	ALI/105[h]			
Long-term:					0.06[i]
Gross alpha and/or gross beta	0.1	0.05			
Specified	ALI/1825[h]	ALI/5475[h]			
OP threat agents (μg/L)[j]	12	4	20	20	20
T-2 toxin (μg/L)	26	8.7	–	–	–
Lewisite: arsenic fraction (mg/L)	0.08[k]	0.027[k]	2	2	2

Footnotes to Table 1.

[a]Long-term (≤1 y) as well as short-term (≤7 d) standards were developed because of the nature of radioactivity and the possibility that radioactive material could be dispersed over a very wide geographic area following a military exchange with nuclear weapons. ALI is the annual limit on intake, and the recommended standards are based on a limit of 1.0 Sv (100 rem) to organs of the GI tract. These exposures should be reduced if exposure via other pathways is occurring.

[b]Field-water-quality standards recommended in this document for adoption by the Armed Forces of the United States are consistent with a pH between 5 and 9, an optimum drinking-water temperature of 60°F ± 10°F (16°C ± 5°C), and a threshold odor number (TON) between 0 and 3. (See Volume 4, Part 1 for further discussion of these parameters.[3])

[c]Reference 1.

[d]Reference 2.

[e]Minimum treatment requirements for assuring potability from Table A of Reference 8. These are short-term consumption provisions that are for "emergency or field operational conditions" and may lead to degraded troop performance and reduced combat efficiency each day they remain in effect.

[f]Recommendations for field-water-quality standards for cyanide from industrial wastewater discharge have been presented in the first part of this volume (see Ref. 3) and there is no evidence to indicate that such standards for cyanide cannot be applied to the threat agent hydrogen cyanide.

[g]If external radiation permits military personnel to occupy a location, then water is considered suitable for consumption for a period lasting up to 7 d.

[h]If specific radionuclides are known to be present, then the annual limit of intake (ALI) should be divided by the stated factors.

[i]A long-term standard (≤1 y) for mixed fission products.

[j]If pretreatment with pyridostigmine bromide is enforced, the recommended concentrations are 4.7 and 1.6 μg/L for 5 and 15 L/d consumption rates.

[k]Based on detection of the arsenic fraction of lewisite in water; the corresponding concentration of lewisite is about 2.75 times greater.

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CHAPTER 2. HYDROGEN CYANIDE

D. W. LAYTON*

OVERVIEW

Hydrogen cyanide (HCN), also referred to as hydrocyanic acid, is a rapidly acting poison that exerts its toxic effects by inhibiting certain enzymes that play a critical role in the use of oxygen for cellular respiration.[1] Once such chemical asphyxiation begins, the nervous and respiratory systems start to fail, and this leads to adverse health effects that can include headache, breathlessness, weakness, tremors, and even death. Because of these toxic properties, HCN gas has been used effectively as a fumigant and for executions in gas chambers.[2] Furthermore, such toxic properties also make HCN a candidate for use as a chemical-warfare agent. In fact, HCN gas was employed by the French during World War I for purposes of chemical warfare.[1,3] However, because cyanide can be detoxified by humans and because HCN is very volatile, massive amounts of the gas are probably needed for it to be effective as a threat agent in chemical warfare.[1] As a threat agent, HCN has also been labeled prussic acid or AC.[2]

According to Sanchis,[4] HCN vapor dispersed as a threat agent will dissolve in water. In the first part of this volume (see Chapter 8 of Volume 4, Part 1[5]). field-water-quality standards were derived for cyanide because cyanide compounds, including HCN, could be found in field water as a result of contamination by industrial wastewaters. Because there is no evidence to indicate that the mode of introduction of HCN into field water will affect its toxicity following ingestion, the short-term field-water-quality standards for cyanide for drinking-water consumption rates of up to 5 and 15 L/d are applied to the threat agent hydrogen cyanide as well.

The (1) general properties, (2) method for detection, (3) pharmacokinetics, and (4) development of standards for cyanide compounds, including HCN, in field water are described in great detail in Part 1 of this volume.[5] The health risks that could occur if the standards are exceeded are presented in Chapter 2 of Volume 9 of this study.[6] Recommended standards for cyanide were calculated using a one-compartment pharmacokinetic model and were based on the assumption that 0.5 mg/L is the

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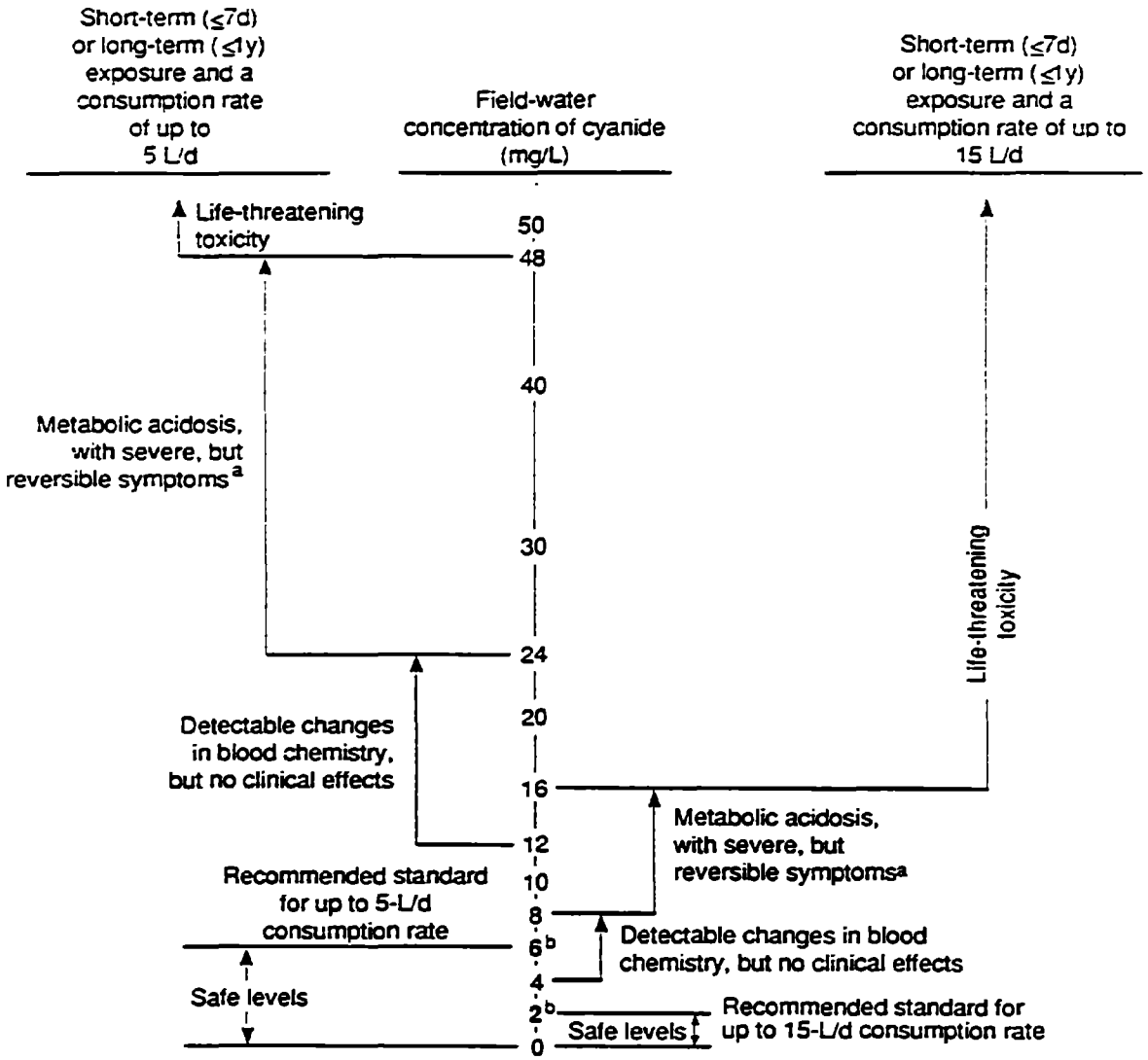
maximum tolerable concentration of cyanide in whole blood. For an assumed water-consumption rate of 5 L/d, the recommended standard for cyanide is 6 mg/L, for a water-consumption rate of 15 L/d. the recommended standard is 2 mg/L.

Figure 1 is taken from Volume 9[6] of this report. It is a visual guide for quickly assessing the impact of cyanide concentrations in field water on the performance of exposed military personnel. This figure shows that ingestion of cyanide concentrations in field water above recommended safe levels can lead to an increased risk of performance-degrading health effects in exposed military personnel. Consequently, the higher the cyanide concentration is above the safe level, the greater the risk that many of the exposed military personnel will develop symptoms that can be performance degrading or even lethal. Unfortunately, the proportion of the exposed military population that could be affected by performance-degrading symptoms, at levels of cyanide above those recommended as standards, cannot be estimated from the available data.



[a]Symptoms of acute cyanide toxicity can include headache, weakness, palpitation, nausea, giddiness, and tremors.

[b]Recommended field-water-quality standard for indicated daily consumption rate and exposure periods up to either 7 d or 1 y.

Figure 1. Health-effects summary for cyanide (from Volume 9[6] of this report).

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CHAPTER 3. RADIOACTIVITY

L. R. Anspaugh*

INTRODUCTION

Radioactivity in water may be derived from a variety of sources. These sources include fallout from nuclear weapons explosions, leaching of naturally occurring radionuclides, and sabotage. In this report we present a discussion of background information concerning radioactivity, analytical methods for detection, and health effects. We conclude by developing recommendations for standards for radioactivity in water appropriate for military use of field-water supplies.

BACKGROUND INFORMATION

DEFINITIONS AND BRIEF REVIEW

Radioactivity is a general term that refers to the transformation of an unstable atom to a different state by the emission of an alpha particle (a ^4He nucleus), a beta particle (an electron), or some other rearrangement of structure. Such a transformation is frequently accompanied by the emission of one or more gamma rays (high-energy photons). For a given radionuclide, this process occurs according to first-order kinetics:

$$\frac{dN}{dt} = -\lambda N \quad , \tag{1}$$

where

N = number of radioactive nuclei;

λ = radioactive decay constant, time^{-1}; and

t = time.

The product λN is referred to as the activity of the radionuclide or sample containing the radionuclide and has units of disintegrations (dis) per unit time.

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Historically, activity has been measured in units of curies (Ci), and 1 Ci was originally defined as the activity of 1 g of ^{226}Ra. This unit was redefined in 1950 so that it could be applied to any radionuclide.[1] It is now the quantity of any radionuclide in which the number of disintegrations per second is 3.700×10^{10}. A more recently defined International System (SI) unit[2] of activity is the becquerel (Bq) and is equal to 1 dis/s. The relationships among units of activity are

$$1 \text{ Ci} = 3.700 \times 10^{10} \text{ dis/s} = 3.700 \times 10^{10} \text{ Bq} \quad .$$

We can describe the amount of a radionuclide present as a function of time by integrating Eq. (1). The result is

$$N = N_0 e^{-\lambda t} \quad , \tag{2}$$

where N_0 is the number of radioactive nuclei when $t = 0$. The half-life of a particular radionuclide is then given by solution of Eq. (2) for t when $N/N_0 = 0.5$. Thus,

$$T_{1/2} = \frac{\ln 2}{\lambda} = \frac{0.693}{\lambda} \quad , \tag{3}$$

Obviously, these relationships of Eqs. (2) and (3) apply to activity as well as to the number of radioactive nuclei. As λN is activity, we can multiply Eq. (2) by λ and then describe the activity as a function of time:

$$\lambda N = A = A_0 e^{-\lambda t} \quad . \tag{4}$$

During the explosion of a nuclear weapon, the fissioning of U or Pu is the major source of resulting activity. Typically, the U or Pu splits into two unstable nuclei that progress through series of decays until stability is regained. No significant alpha-emitting radionuclides are created by this process, but the residual U or Pu does emit alpha particles. Initially, several hundred radionuclides are created, but these decay rapidly (have short half-lives). Over time, the gross activity (sum of all radionuclides) may be approximated by the relationship[3]

$$A = A(1)t^{-1.2} \quad , \tag{5}$$

where A(1) = activity when t = 1 h, i.e., H + 1, and the H indicates the time when the detonation occurred and that the number following is in units of hours.[a]

If entry is made into an area contaminated with nuclear fallout, soldiers will encounter an external gamma-exposure field that results from the emission of gamma rays by the disintegrating radionuclides. Such exposure rates are measured by survey meters and refer to the number of ion pairs (or charge) created per unit volume of air per unit time. The exposure rate X as a function of time is also approximated by Eq. (5), with X and X(1) substituted for A and A(1). The exposure is the integral over time of the exposure rate and has units of charge per unit volume or weight of air. The special unit of exposure is the roentgen (R) and is defined as that amount of gamma radiation that will produce 1 electrostatic unit of charge of either sign per cm^3 of air at standard conditions.[2]

If a soldier enters a radiation field at m hours after the detonation and remains until n hours after the detonation, we may approximate his exposure (X) by integrating the exposure-rate analog of Eq. (5):

$$X = \int_m^n \dot{X}\, dt = \frac{X(1)}{0.2}\left(m^{-0.2} - n^{-0.2}\right) , \tag{6}$$

Normally, we would not have measured X(1), but would have measured X(t) at some time other than t = 1. X(1) is then approximated by

$$X(1) = X(t)t^{1.2} . \tag{7}$$

Radiation dose (D) is defined as the amount of energy absorbed per unit mass of tissue. The special unit[2] of radiation dose is the rad, which is equal to 100 ergs/g. The newer SI unit is the gray (Gy), which is equal to 1 J/kg. Thus, 1 Gy = 100 rads.

It was noted early in the study of radiation effects on cellular and mammalian systems that some radiations, such as neutrons and alpha particles, produced much greater biological effects than did equal doses of beta particles or gamma rays. This led to the definition of a dose-equivalent unit, H, which is equal to the dose multiplied by Q, the quality factor, and N, the product of all other modifying factors.[a] The special unit

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[a] The reader is cautioned that the symbol H by itself has an entirely different meaning than the H in H + 1. This possible confusion is regrettable, but these usages conform to the standard nomenclatures in two separate areas of health physics.

of dose equivalent is the rem, and the newer SI unit is the sievert (Sv).[2] The sievert is also defined as equal to 1 J/kg as both Q and N are unitless. Thus, 1 Sv = 100 rem. Current recommendations[4,5] are to assign a value of 1 to N and these values to Q:

Q = 1 for beta particles, electrons and all electromagnetic radiation including gamma radiation, x rays and bremsstrahlung,

Q = 2.3 for thermal neutrons,

Q = 10 for protons and singly-charged particles of rest mass greater than one atomic mass unit of unknown energy,

Q = 20 for fast neutrons, alpha particles, and multiply-charged particles (and particles of unknown charge) of unknown energy.

In 1977 the International Commission on Radiological Protection (ICRP) issued its Publication 26,[6] which contained a major new concept in radiation protection. This new concept was based on the proposal that risk, and not dose or dose equivalent, should be limited. This was implemented by the creation of the quantity now known as <u>effective dose equivalent</u>,[4] H_E. This is defined by the following equation:

$$H_E = \sum_T H_T w_T \quad , \tag{8}$$

where

H_T = the dose equivalent in tissue (T), and

w_T = a weighting factor representing the proportion of the risk resulting from tissue (T) to the total risk, when the body is irradiated uniformly.

Risk in this context is taken to be the long-term stochastic risk of developing genetic defects or cancer. The values of w_T recommended by the ICRP are shown in Table 1.

For the "remainder" category, the ICRP recommended that a w_T of 0.06 be assigned to each of the 5 organs or tissues of the remainder (i.e., organs or tissues not listed explicitly in Table 1) receiving the highest dose equivalents, and that all other tissues or organs can be neglected. The ICRP further stated that, when the gastrointestinal tract is irradiated, the stomach, small intestine, upper large intestine,

Table 1. Weighting factors recommended by the ICRP[6] for use in calculating effective dose equivalent.

Tissue	w_T
Gonads	0.25
Breast	0.15
Red bone marrow	0.12
Lung	0.12
Thyroid	0.03
Bone surfaces	0.03
Remainder	0.30

and lower large intestine be treated as four separate organs.[6] In a later clarification, the ICRP made clear that it did not intend that the hands and forearms, the feet and ankles, the skin and the lens of the eye to be included in the "remainder", and that these tissues should therefore be excluded from the computation of effective dose equivalent.[4]

This new concept has been widely adopted in Europe, but has only recently gained acceptance in the United States. On January 20, 1987, President Reagan approved a new Radiation Protection Guidance to Federal Agencies for Occupational Exposure.[7] This new guidance was developed under the leadership of the Environmental Protection Agency (EPA), but was stated to be a cooperative effort of the Nuclear Regulatory Commission (NRC), the Occupational Safety and Health Administration, the Mine Safety and Health Administration, the Department of Defense, the Department of Energy, the National Aeronautics and Space Administration, the Department of Commerce, the Department of Transportation, the Department of Health and Human Services, and the Environmental Protection Agency. This new guidance states that ". . . it is appropriate to adopt the general features of the ICRP approach in radiation protection guidance to Federal agencies for occupational exposure."

The NRC has also moved to bring its regulations for its licensees into line with the concept of effective dose equivalent as put forth by the ICRP. This process was started in 1980 and a complete proposed replacement for its "Standards for Protection Against Radiation" was published in 1986.[8] While not yet approved, these proposed standards are stated to be intended to put into practice many of the newer recommendations of the ICRP and to be consistent with the the planned [but at that time not yet approved] Presidential guidance for Federal agencies.

The above dose concepts are most easily visualized when considering very brief exposure to radiation of origin external to the body. However, when radionuclides are inhaled or ingested, they typically will locate preferentially in one or more organs and they may stay there for a substantial period of time. This complicates the usual concept of dose (or risk) limitation, which is usually considered on a yearly basis, because radionuclides taken into the body in a year's time may not produce the resulting dose for many years. In order to provide a means of regulating the dose resulting from the inhalation or ingestion of radionuclides, the ICRP has defined the committed dose equivalent. This is the ". . . time integral of the dose-equivalent rate in a particular tissue that will be received by an individual following an intake of radioactive material into the body. The Commission has set the integration time as 50 y after the intake, taken to correspond to a working lifetime."[4]

As a logical extension, the committed effective dose equivalent is the committed dose equivalent for each organ weighted as explained above. "To avoid ambiguity in defining the remainder tissues, the time integration should be carried out before selecting the relevant tissues for the summation."[4]

OCCURRENCE OF RADIOACTIVITY IN NATURAL WATERS

Many radionuclides occur naturally in the environment, either because their half-lives are the within orders of magnitude of the age of the earth (e.g., ^{40}K, ^{232}Th, ^{235}U, and ^{238}U); they are daughter radionuclides of their long-lived Th and U parents (e.g., ^{234}U, ^{230}Th, ^{228}Ac, ^{228}Th, ^{226}Ra, ^{222}Rn, ^{220}Rn, ^{210}Pb, and ^{210}Po); or they are created by cosmic-ray interactions in the atmosphere (e.g., ^{3}H, ^{7}Be, and ^{14}C).[9]

Each of the above and many other radionuclides occur in water, but the most important ones are ^{238}U and its daughters, ^{232}Th and its daughters, and ^{40}K.

The ^{40}K constitutes 0.0117% of all potassium and is, therefore, a common constituent of water, particularly seawater. Seawater contains 300 pCi/L of ^{40}K.[9]

Data on the occurrence of uranium in domestic, surface, and ground water have been summarized by Drury et al.[10] Their summarized data for the entire United States are shown in Table 2. The total range is nearly five orders of magnitude.

The parent radionuclide, ^{232}Th, occurs in soils and rocks with about the same activity density as does ^{238}U.[9,11] However, ^{232}Th is highly insoluble in water and it apparently occurs only at very low concentrations.[12]

Table 2. Summary of the occurrence of uranium in U.S. waters.[10]

Type of water	Number of water samples	Range (pCi/L)	Mode (pCi/L)
Domestic	28,239	0.01 to 653	0.1 to 0.2
Surface	34,561	0.01 to 582	0.2 to 0.5
Ground	55,433	0.01 to 653	2 to 5

Most of the attention concerning the occurrence of radionuclides in water has centered around radium, both ^{226}Ra and ^{228}Ra. These are decay products of ^{238}U and ^{232}Th, respectively. Until recently, ^{226}Ra had been more thoroughly studied than ^{228}Ra. The occurrence of both radionuclides in drinking water in the U.S. has been reviewed by Hess et al.[13] as part of a survey to assess problems in meeting the EPA interim drinking water standard for radium of 5 pCi/L.[12] Results reported by Hess et al. are that there are approximately 200 reported public water suppliers with ^{226}Ra in excess of 5 pCi/L after normal treatment. For surface waters, the Ra content is generally low; the concentration of ^{226}Ra generally ranges between 0.1 and 0.5 pCi/L and the activity ratio of $^{228}Ra/^{226}Ra$ is generally more than 1. The results of detailed studies of ground water are shown in Table 3. Some mineral waters from European countries have been noted to contain concentrations of ^{226}Ra that range up to 50 pCi/L.[11]

ANALYTICAL METHODS

Many methods exist for measuring radiation and radioactivity. This section will only describe the measurement of radioactivity in water. The contaminant of greatest concern to the military is probably fallout from nuclear weapons. However, consideration must be given also to deliberate contamination of water with other radioactive materials and to the possible presence of large amounts of naturally occurring radionuclides, such as U and Th and their daughters. Thus, it is strongly desirable to have a method that can measure both alpha and beta emissions. Alpha emissions are typically more difficult to measure because of the small amount of mass required to completely absorb them (a sheet or two of paper is sufficient).

Table 3. Summary of ^{228}Ra and ^{226}Ra distribution in ground water by aquifer type for the Atlantic Coastal Plain and Piedmont provinces. The data were taken directly from Ref. 13.

		^{228}Ra		^{226}Ra	
Aquifer type	n[a]	Geometric mean (pCi/L)	Range (pCi/L)	Geometric mean (pCi/L)	Range (pCi/L)
Igneous rocks (acidic)	42	1.39	0.0 to 22.6	1.80	0.0 to 15.9
Metamorphic rocks	75	0.33	0.0 to 3.9	0.37	0.0 to 7.4
Sand	143	1.05	0.0 to 17.6	1.36	0.0 to 25.9
Arkose	92	2.16	0.0 to 13.5	2.19	0.0 to 23.0
Quartzose	50	0.27	0.0 to 17.6	0.55	0.0 to 25.9
Limestone	16	0.06	0.0 to 0.2	0.12	0.0 to 0.3

[a] n = number of samples.

Several measurement methods are described in the 15th Edition of Standard Methods for the Examination of Water and Wastewater.[14] For the measurement of total gross alpha and total gross beta radioactivity, the preferred method is to dry a sample of water and to insert the residue inside a gas-flow proportional counter. The counts are then recorded. By varying the voltage applied to the proportional counter, either alpha activity alone may be measured or alpha plus beta activity. Such measurement systems can be made into small, rugged packages, although a supply of counting gas must be carried.

Another simpler but less sensitive device can be used. Such a device is the thin-window proportional counter, which may be used to count samples outside of the counter. It is therefore less sensitive because the alpha particles must penetrate an air path and the window in order to be counted. The advantage is that a supply of counting gas is not required.

At least for fixed installations, many other methods of analysis could be used. These include the direct counting of the water with the use of a sodium-iodide or, preferably, a germanium spectrometer to measure the energy of gamma rays emitted by most decaying radionuclides. The latter system has the powerful advantage of being able to identify exactly what gamma-emitting radionuclides might be in the water.

At present, the U.S. Army does not have a field-portable device for measuring quantitatively the radiological contamination of field-water supplies; and the only measurement device available is a Geiger counter with a rubber sleeve that can be dipped in the water.[15,16] This technique has been described by Lindsten.[17,18] The recommended procedure for measuring beta-emitting radionuclides in water is to use the Army Field Radiacmeter PDR-27, which is basically a field-survey meter that uses a Geiger-Muller tube for the detector. The details of the procedure[17,18] are

1. Separate the two (2) detector heads on the PDR-27 meter.
2. Remove the beta shield from the sensitive (larger) detector probe.
3. Cover the sensitive (larger) detector probe with a thin rubber sheath to protect it from the water.
4. Turn the range switch to BATT COND. The meter should read to the right of the halfway mark; indicated on the meter. If not, replace the batteries.
5. Insert the protected probe into the water to be measured.
6. Read the PDR-27 meter scale in mR/hr.
7. Refer to the conversion chart (taken from Ref. 18 and reproduced here as Fig. 1) to convert from mR/hr to pCi/L.

The conversion chart is stated to be based upon experiments that were conducted with actual mixed fission products from Operation Sunbeam carried out at the Nevada Test Site,[17,18] but very few details of this experiment are provided. As Operation Sunbeam was conducted in 1962,[19] or about 27 y ago, it would be more comforting to have a more recent confirmation of this detection capability. Even more desirable would be a modern instrument designed for the purpose of monitoring water supplies.

While the PDR-27, if properly calibrated, should be sufficient to protect against water that has been contaminated by nuclear fallout, it would be totally inadequate to protect against alpha-emitting radionuclides. Such radionuclides can occur in water at high concentrations due to purely natural causes or may be placed in water as agents of sabotage. Lindsten[17] has stated that the Army does have two instruments capable of measuring alpha-emitting radionuclides; these are the IM-170/PDR-60 and the IM-160F/PDR-56. Either could be used to count alpha activity from the residue of a water sample that has been evaporated to dryness. Lindsten[17] discusses some problems in making such measurements, and concludes that, "In spite of the problems, research should be conducted on the use of the two available alpha radiacmeters for measuring radium-226 in water."

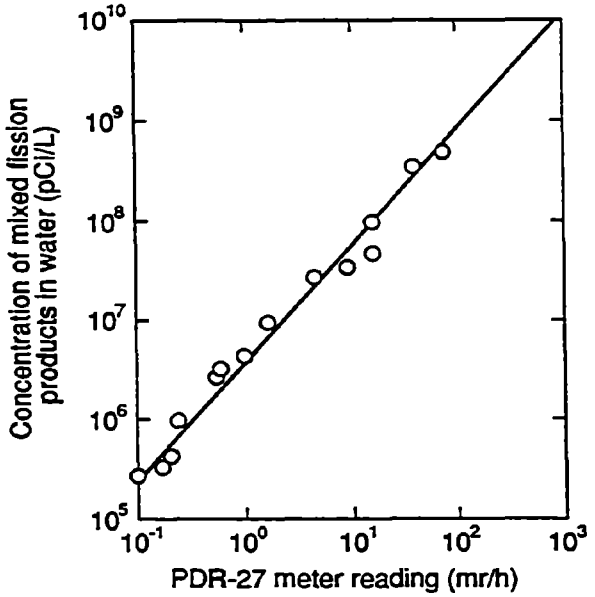

Figure 1. Conversion of PDR-27 meter reading to concentration of mixed fission products in water (from Ref. 18).

HEALTH EFFECTS OF RADIATION

There are many possible health effects that might result from exposure to radiation. In this discussion, we will follow the lead of the ICRP[6] and divide these effects into those described as either "stochastic" or "non-stochastic." Accordingly, stochastic effects are those for which the probability of an effect occurring, rather than its severity, is regarded as a function of dose, without threshold. Such stochastic effects are mainly those of carcinogenesis and mutagenesis; these occur with low probability and might be evident only years after exposure. According to the instructions given with regard to the present task of developing the basis for field-water-quality standards, such effects are not to be considered. They will, however, be briefly discussed below.

Non-stochastic effects are those for which the severity of the effect varies with dose, and for which a threshold may therefore occur. Such effects include those against which the Army wishes to protect and include incapacitation (due to, e.g., vomiting) and death. (Death, of course, does not become increasingly severe with an increase in dose, but survival time does decrease with increasing dose.) The criteria for field-water quality to be developed below are based primarily upon avoiding incapacitation. Thus, a primary goal of the material presented here is to develop a risk analysis for the incapacitating non-stochastic effects of radiation.

All aspects of the effects of radiation on human health have been comprehensively reviewed recently by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR).[11] Another major review that had the goal of providing quantitative models to predict effects was that of Evans et al.,[20] which was done for the NRC.

NON-STOCHASTIC EFFECTS

The non-stochastic, or acute, effects of radiation are well described in the book Radiation Injury by Upton.[21] Other reviews of major interest include those of the National Council on Radiation Protection and Measurements (NCRP),[22] Lushbaugh,[23] and Anno et al.[24] for the Defense Nuclear Agency. More limited reviews were done by the ICRP[25] on the effects on organs and the recent quantitative treatment by Scott et al.[26] of bone-marrow syndrome lethality in humans.

One obvious goal of a standard for water quality is to guard against acute lethality. Since 1944, there have been a large number of accidents with radiation and the experience from the atomic bombings of Japan. On the basis of these data for exposures occurring over a very brief time period, the UNSCEAR[11] has estimated that the midline (i.e., the midline of the human body) radiation dose that would kill 50% of those receiving it within 60 d is 2.5 Gy (250 rad) or more. This number (i.e., the radiation dose that would affect 50% of those receiving it) is hereinafter denoted D_{50}. (Note that we are specifically referencing the dose to the midline of the body. Some reports refer to the free-in-air dose, which is about 1.5 times higher than the midline dose.)

After reviewing similar data and data concerning effects observed in larger animals, Scott et al.[26] concluded that the D_{50} for acute lethality in humans is 2.6 ± 0.12 Gy. Scott et al.[26] (see also Ref. 27, which is a Chapter by Scott and Hahn in Ref. 20) have used the Weibull model to describe the probability of death and other acute effects following exposure to radiation. The general form is that

$$\text{Risk} = 1 - e^{-Z} \tag{9}$$

where Z is the hazard function and is given by

$$Z = \ln(2) \left(\frac{D}{D_{50}}\right)^V \tag{10}$$

where D is the dose for which we wish to evaluate the risk and V is the "shape parameter." From the examination of 161 data points from the study of effects on mammals, Scott et al.[26] have derived a value for V of 10.0 ± 0.05. Thus, for humans the probability of mortality following radiation exposure during a brief period can be calculated with Equations (9) and (10) with the values for D_{50} and V of 2.6 Gy and 10, respectively. The results are as shown by the curve labelled "acute exposure" in Fig. 2.

There is also a substantial data base on the exposure of animals (and, in a few cases, man) to fairly high doses, but at low dose rates over very long time periods. In this situation, recovery is clearly occurring while the exposure is continuing. In one experiment with dogs, it was noted that the D_{50} increased by a factor of 4 when the dose rate was 0.33 Gy/d. Scott et al.[26] have examined the relationship between D_{50} and dose rate as based upon experimental data for mammals. The goal was to develop a function $\theta(\dot{D})$ that describes the D_{50} as a function of the dose rate $\dot{D}$. The model derived by Scott et al.[26] that best fits the data is

$$\theta(\dot{D}) = \theta_1/\dot{D} + \theta_\infty \quad , \tag{11}$$

where θ_1 and θ_∞ are parameters that depend upon the species and the units of dose and dose rate. The parameter θ_∞ is the value of D_{50} for very high dose rates. For man, Scott et al.[26] have provided their best estimates of 0.05 ± 0.02 Gy^2/hr for θ_1 and of 2.6 ± 0.12 Gy for θ_∞.

For situations where the dose rate is not constant, it is useful to accumulate the dose X in units of D_{50} ($X = D/D_{50}$) where D_{50} is not necessarily constant. In this case, Scott et al.[26] have provided the following equation for the normalized dose increment dX in the small exposure time interval dt when exposed to the dose rate $\dot{D}(t)$:

$$dX(t) = \dot{D}(t)\theta(\dot{D})^{-1}dt \tag{12}$$

For exposure to fallout, both $\dot{D}(t)$ and $\theta(\dot{D})$ would be changing fairly rapidly. $\dot{D}(t)$ would be changing as according to Equation (5) and θ according to Equation (11). This problem has been solved by numerical integration in order to evaluate the risk of death from exposure to radiation from a fresh fallout field. The results of the calculation are shown as the curve labelled "protracted exposure" in Fig. 2. In this case the dose units along the abscissa are for the dose to be accumulated over infinite time when exposure starts one hour after the detonation. (The infinite dose of 5 Gy corresponds to an initial dose rate at H+1 of 1 Gy/h.) As a result of the protracted exposure, the D_{50} has about doubled.

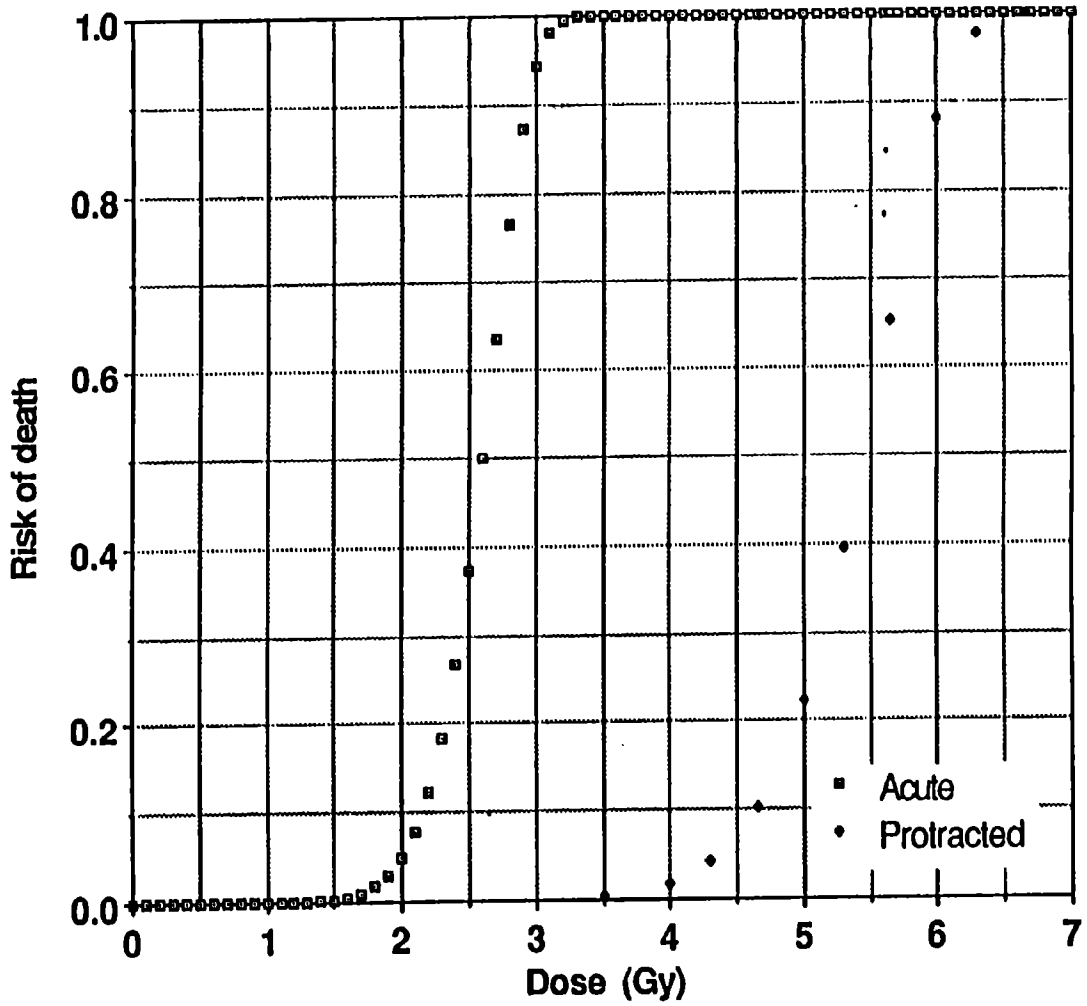

Figure 2. Risk of death for acute exposure and for protracted exposure from a fallout field. The curve for protracted exposure was calculated for the hypothetical case of an individual entering a fallout field at H + 1 h and staying there for infinite time.

Effects that would impair the capacity of personnel to perform their duties should be expected at doses below the D_{50} for acute lethality. The symptoms that have been observed include anorexia, nausea, fatigue, vomiting, and diarrhea. These effects are generally known as the prodromal syndrome and they are listed in order of occurrence with increasing dose. Here, we presume that the effects of anorexia, nausea, and fatigue are nuisances that are not incapacitating, but that vomiting and diarrhea are incapacitating. Authoritative sources have made a variety of statements concerning the probable occurrence of these effects. The ICRP[28] has stated, "Vomiting would not be expected for whole body doses less than 0.5 Gy." In a previous publication,[29] the ICRP had indicated that vomiting would be expected at a frequency of 5% following a dose of 100 rad (1 Gy) and a frequency of 50% following a dose of 200 rad, with the expected time of occurrence of nausea and vomiting at 3 h post exposure. The UNSCEAR[11] has also stated that vomiting is noted to be infrequent at doses below 1 Gy. The NCRP[22] has considered the effects of radiation on work capacity and has stated that most authorities agree that brief whole-body exposures of 200 R (equivalent to a midline dose of about 130 rad or 1.3 Gy) would not affect the performance capability of the average adult. These statements are generally consistent with the quantitative relationships that have been developed by Lushbaugh[23] and modeled more extensively by Scott and Hahn.[27]

Scott and Hahn have used the same type of hazard and risk functions as those noted above for acute lethality in Equations (9) and (10). The relevant values for D_{50} and V are shown in Table 4.

Two situations are known to be of interest. The first is for exposure occurring in a short period of time, and the second is for the somewhat protracted exposure that might be experienced in a fresh fallout field. The latter situation can be considered by calculating the fraction of dose within a 7-d period that would be accumulated during the first 24 hours versus that accumulated during the next 6 d. This is done by calculating the integral indicated in Eq (6) for each of the two time periods and then calculating the fraction of the total dose accumulated during each of the two periods. The result is that 73% of the dose would be delivered during the first day. The hazard function for vomiting for each total dose D would be

$$Z = 0.693 \left(\frac{0.73D}{1.8} + \frac{0.27D}{4.9}\right)^3 \quad .$$

Table 4. Median dose estimates (D_{50}) and shape parameters (V) for prodromal symptoms after total body exposure.[27]

Symptom	Parameter	Time period of dose accumulation (Days)	
		0–1	1–7[a]
Anorexia	D_{50} (Gy)	0.97	2.0
	V	2	[2]
Nausea	D_{50} (Gy)	1.4	2.6
	V	2	[2]
Fatigue	D_{50} (Gy)	1.5	ND[b]
	V	2	[2]
Vomiting	D_{50} (Gy)	1.8	4.9
	V	3	[3]
Diarrhea	D_{50} (Gy)	2.3	5.3
	V	2	[2]

a Brackets indicate that values were assumed by Scott and Hahn to be the same as those for the 0–1 d period.

b ND = Not determined.

The results for the two sets of calculations are shown in Fig. 3. In this case the D_{50} has increased from 1.8 Gy to 2.2 Gy for the more protracted exposure. It is also of interest that the predicted incidence of vomiting is about 5 to 10% at 1.0 Gy (100 rad) for either situation. We have not plotted the expected incidence of diarrhea, as this would be an additional incapacitation only at doses beyond those projected to cause vomiting.

The occurrence of these gastrointestinal prodromal symptoms is complex. It has been noted by the UNSCEAR[11] that these effects are mediated through the autonomic nervous system, and these effects can be produced by partial body irradiation of the head, thorax, or abdomen, with the abdomen being the most sensitive. Thus, we presume that ingested radionuclides would also produce these symptoms; however, there is no direct observation of these effects in humans being produced by ingested radionuclides.[27]

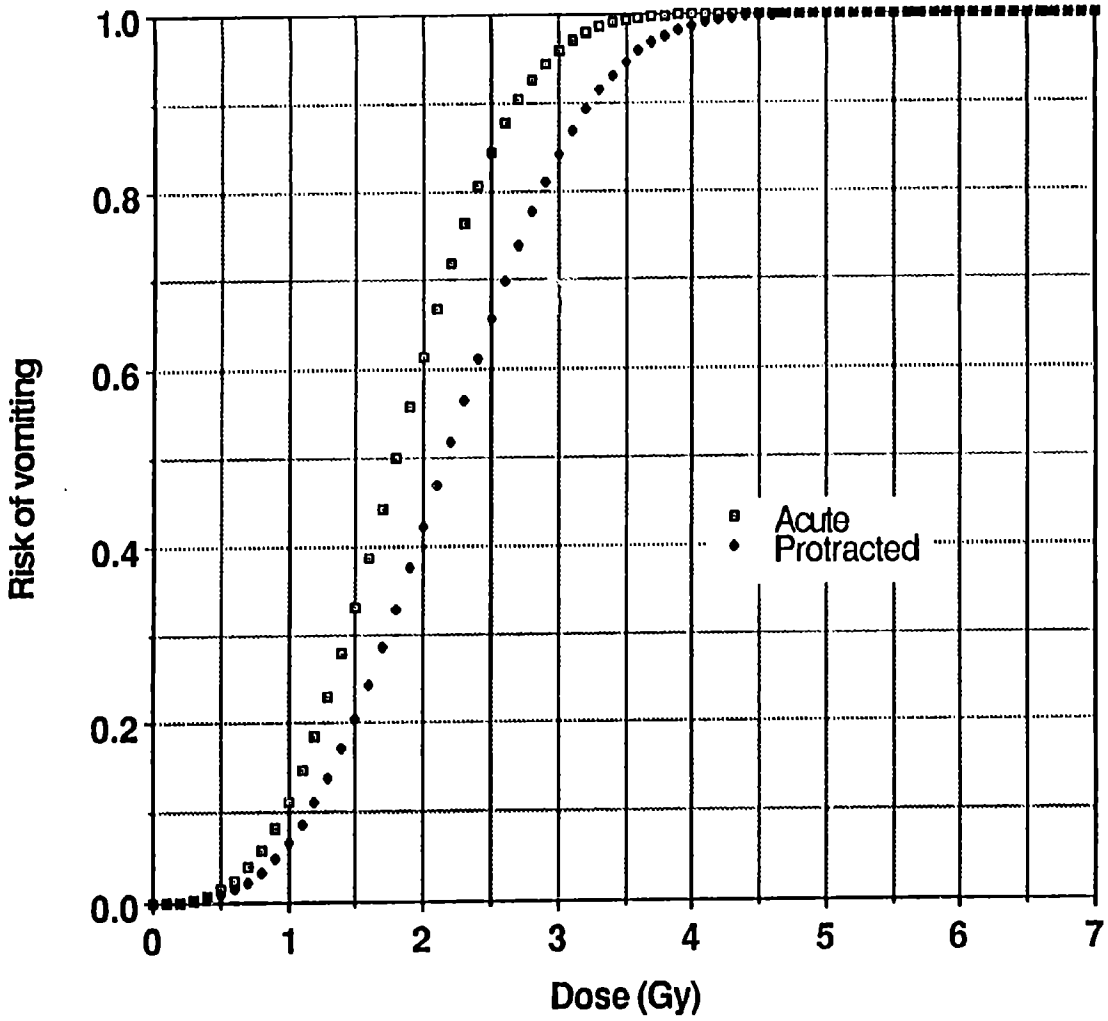

Figure 3. Risk of vomiting for acute exposure and for protracted exposure from a fallout field. The curve for protracted exposure was calculated for the hypothetical case of an individual entering a fallout field at H + 1 h.

Following the prodromal phase, a symptom-free latent phase would ensue but would be followed approximately 3 wk later by the main illness (if any occurs), caused by depression of the number of circulating blood cells. Following doses of about 1.0 Gy (100 rad), complete recovery of virtually all personnel would be expected within 6 to 8 wk following exposure.

At supralethal doses in the range of 10 to 50 Gy (1000 to 5000 rad), death would occur in a week or less from denudation of the gastrointestinal tract. At doses above 5000 rad, survival time is inversely related to dose, and incapacitation is immediate due to disruption of the central nervous system.

Another analysis of this general problem has been carried out over many years by the members of the Department of Defense (DOD) Intermediate Dose Program. The results of their analyses have been published[30] and are reproduced in Figs. 4 and 5. The essential results are very similar to those depicted in Fig. 3; performance would be expected to be degraded following doses of 1 to 2 Gy (100 to 200 rad), and this would occur at a few hours after exposure.

DELAYED EFFECTS

The delayed effects of radiation (or of any other contaminant in military field-water supplies) are not at issue in the current context. However, the delayed effects of radiation are discussed briefly to provide some perspective.

The significant delayed effects are carcinogenesis and induction of genetic defects. Both have received much attention by the research community, and both effects have been reviewed by the National Academy of Sciences-National Research Council Committee on the Biological Effects of Ionizing Radiation (BEIR).[31]

That radiation can cause cancer in human populations has been demonstrated in several study groups that have received radiation in amounts far in excess of natural background. However, the overall effect (in a population sense) is small and can be demonstrated only if a rather large population is available for study. Thus, there are still uncertainties about predicting the effects for a population exposed to relatively lower doses. This is because of two general problems. First, there is uncertainty in the shape of the dose-response curve. Second, because no large human population has yet been followed throughout its collective lifetime, there is uncertainty whether radiation acts to increase the absolute risk or the relative risk. (An absolute risk refers to the induction of a fixed number of cancer cases per unit dose, whereas a relative risk refers to a fractional increase in the background rate per unit dose.) This makes a substantial difference, as the background rate of cancer incidence increases exponentially with age.

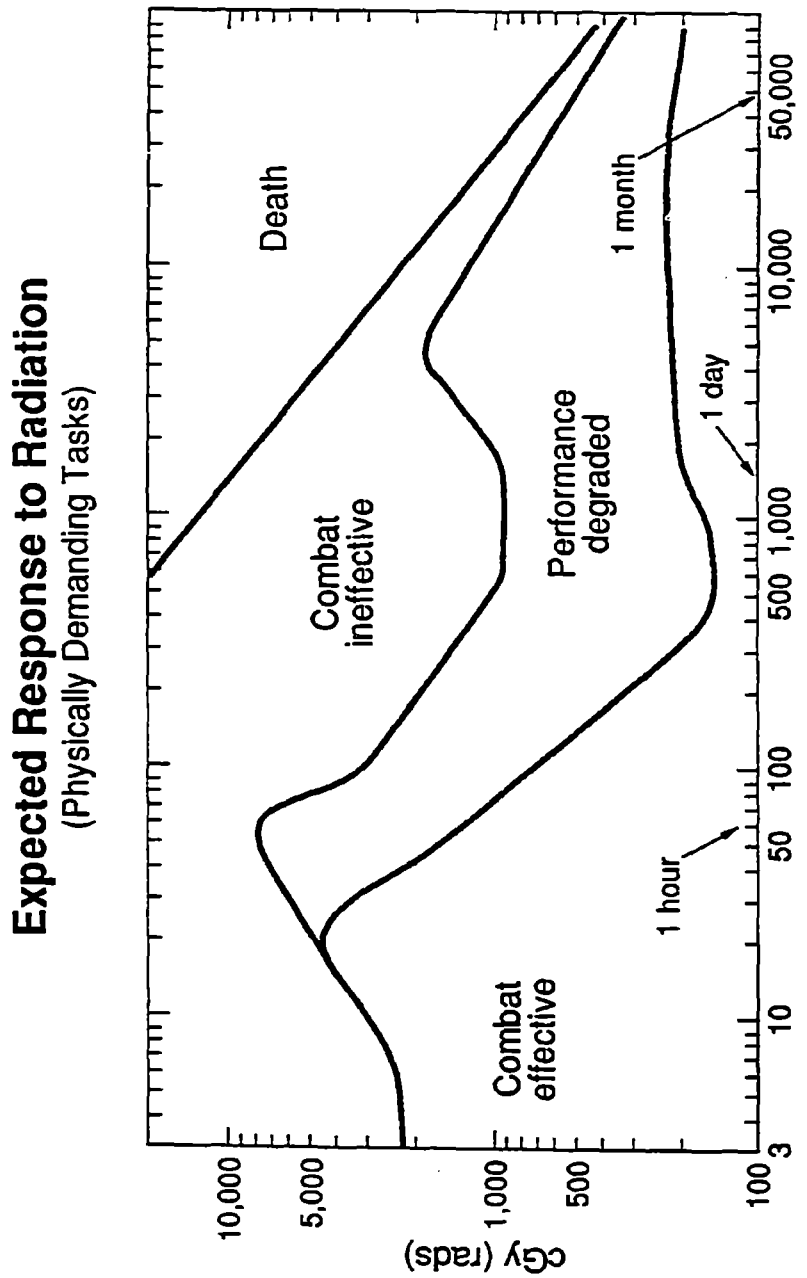

Figure 4. Expected response to radiation for physically demanding tasks (from Ref. 30).

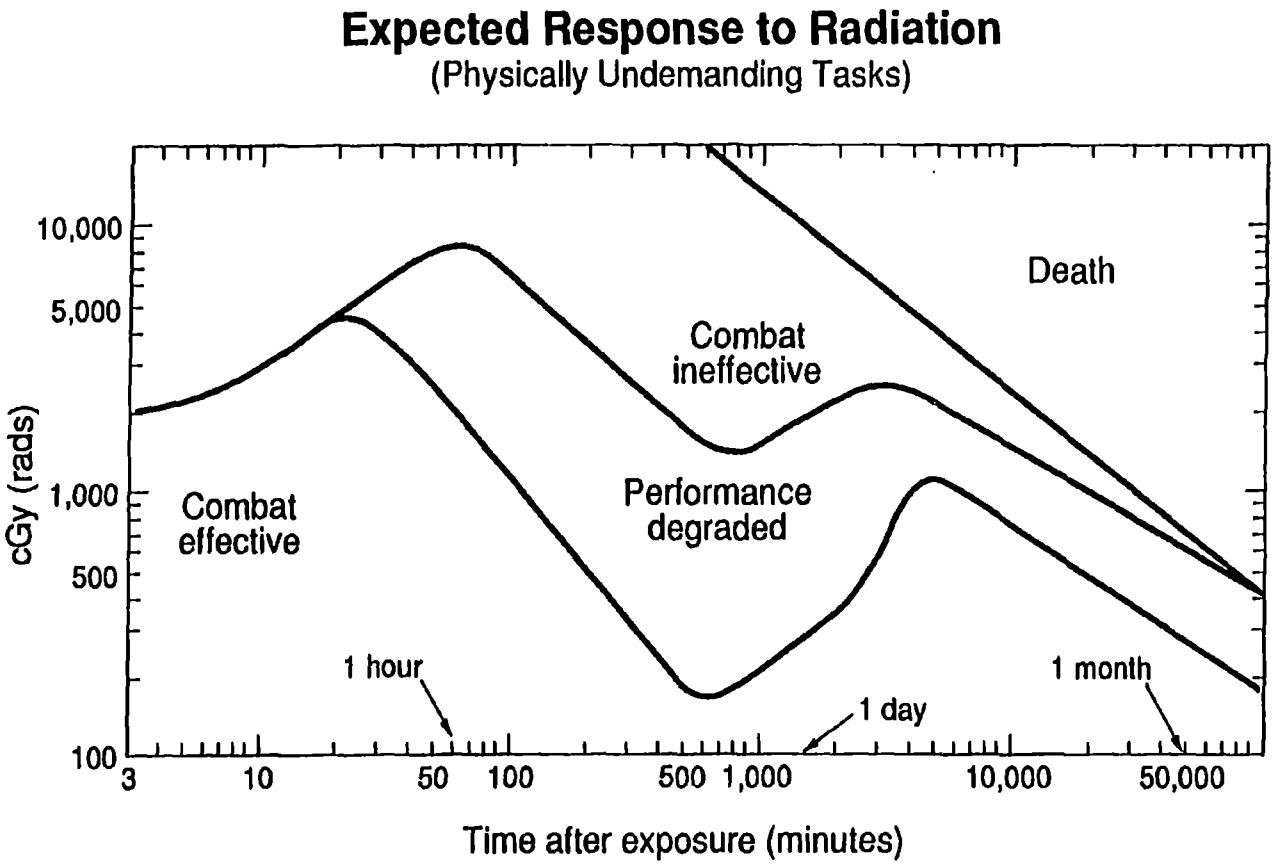

Figure 5. Expected response to radiation for physically undemanding tasks (from Ref. 30).

The BEIR Committee[31] estimates that, for a minimum dose of 10 rad (0.1 Gy), the excess mortality from all forms of cancer would occur at a rate between 9.5×10^{-6} and 5×10^{-4} per person per rad. This estimate is specific for low linear-energy-transfer radiation, which is that specified for Q = 1. In this context, therefore, it is reasonable to assume that the above risks would be the same if expressed on a per rem, rather than per rad, basis.

The situation is less clear for genetic effects, "because radiation-induced transmitted genetic effects have not been demonstrated in man."[31] Such effects have been shown in the mouse, however, and extrapolations are based on these data and other basic knowledge.

The BEIR Committee[31] estimates that, for 1 rem (0.01 Sv) of parental exposure throughout the general population, the risk of additional serious genetic disorder is between 5×10^{-6} and 7.5×10^{-5} per live birth per rem. An exposure of 1 rem received in each generation is projected, when genetic equilibrium is established, to result in an increased risk of 6×10^{-5} to 1.1×10^{-3} per live birth per rem.

For comparison, the background risk of mortality from cancer is 0.16 per person, and the background risk of serious disorder of genetic origin is 0.1 per live birth.

CURRENT ARMY STANDARDS

The present U.S. Army standards for radioactivity in field-water supplies are given in Publication TB MED 577.[32] For the short-term radiological standard, the statement is given that, "There are no concrete radiological standards. It has been assumed that water is suitable for drinking if personnel can occupy the area around the water source for a week or less without adverse physiological effect." For the long-term standard, the statement given is, "There are no concrete radiological standards. There is not yet enough data to set a practical long-term standard."

The U.S. is also a party to international agreements with the North Atlantic Treaty Organization (NATO). NATO field-water-quality standards are proposed in the draft document STANAG-2136.[33] For radiological activity, the minimum requirements are 150 Bq/mL (4.1 μCi/L) for short-term consumption and 10 Bq/mL (0.27 μCi/L) for long-term consumption. The additional statement is made that these values should be proportionately lowered, if the rate of consumption should exceed 5 L/d. The U.S. is also part of the Quadripartite Standardization Agreement with the British, Canadian, and Australian Armies. Standards for field water-quality are contained in the document

QSTAG-245.[34] The only radiological standard given is for mixed fission products. For source water (water before treatment), it is stated that the numerical standard is "To be determined." For short-term consumption of drinking water, this statement is provided

(a) Areas Having Received Fallout

For short-term consumption (up to 7 d) no absolute maximum tolerance is recommended or considered necessary. This is based on the consideration that if the risk of external radiation from fallout is such as to allow the source to be used, then the water will be suitable for drinking during occupancy not exceeding one week.

(b) Areas Not Having Received Fallout

For short-term consumption (up to 7 d) any water source showing a reading above background, as measured with a dose rate meter or other suitable method, should only be used if no better source is available and the use is essential. This is based on the consideration that personnel should not be subjected to unnecessary radiation exposure.

For long-term consumption, QSTAG-245 provides a standard of 0.06 μCi/L (2.2 Bq/mL) for mixed fission products; this value is also to be reduced proportionately, if the water consumption should be above 5 L/d. The QSTAG value is about 5 times lower than that proposed for NATO.

The three sets[32,33,34] of standards are incomplete and/or inconsistent. For short-term use of field supplies, it is clear that the primary intent has been to deal with contamination that would result from nuclear fallout. Standards to protect against "poisons of opportunity" and high concentrations of naturally occurring radionuclides are lacking, except in the NATO draft document that simply lists "Radiological activity." Standards in QSTAG-245 are of recent vintage, but only address mixed fission products.

DEVELOPMENT OF PROPOSED STANDARDS FOR RADIONUCLIDES IN WATER

In the following pages, we will consider standards for the short-term and long-term use of field-water supplies. Short-term is defined as 7 d or less and long-term is defined as $\leq$1 y. We also assume two different levels of water consumption: 5 L/d and 15 L/d. The reader is cautioned that the recommendations will be developed under the assumptions that only short-term performance degradation is of significance under emergency conditions, and that the only exposure occurring is via water consumption. If external exposure and inhalation of radionuclides are also occurring, then proper allowance must be made for these exposure mechanisms.

THE ICRP METHODOLOGY

Because the methodology of the ICRP is generally accepted throughout the world, it seems desirable to adapt this very large body of accumulated knowledge in developing proposed standards for field-water quality for the Army. One distinct advantage of this approach is that other parties with whom the U.S. has agreements will likely accept the ICRP methods as an appropriate foundation for standards.

The basic principles of radiation protection espoused by the ICRP are these[6]:

1. No practice shall be adopted unless its introduction produces a positive net benefit;

2. All exposures shall be kept as low as reasonably achievable, economic and social factors being taken into account; and

3. The dose equivalent to individuals shall not exceed the limits recommended for the appropriate circumstances by the Commission.

Within this context, the ICRP has established limits of intake for occupational workers to limit both the committed effective dose equivalent and the committed dose equivalent to an organ. The limit for the committed effective dose equivalent is 0.05 Sv (5 rem) per year and is intended to limit the stochastic (carcinogenesis and mutagenesis) effects. The limit for the committed dose equivalent to an organ or tissue is 0.5 Sv (50 rem) per y and is intended to limit the non-stochastic effects.

The ICRP has recognized that infrequent situations may arise where it may be necessary to permit workers to exceed the basic limits. In such circumstances, the ICRP[6] has stated that such exposures ". . . may be permitted provided that the dose-equivalent commitment does not exceed twice the relevant annual limit in any single event, and, in a lifetime, five times this limit." This is equivalent to permitting the intake of radionuclides corresponding to a committed dose equivalent for an individual tissue or organ of 1 Sv (100 rem) for a single event.

In order to ensure that the Commission's primary committed dose-equivalent limits are not exceeded, a great deal of effort has been devoted to understanding the metabolism of ingested radionuclides. The primary result of these efforts has been the publication of exposure-to-dose conversion factors for both inhalation and ingestion. These factors are then used to derive secondary limits, which for ingestion, are known as Annual Limits on Intake (ALI).

U.S. ADOPTION OF THE ICRP METHODOLOGY

The EPA has recently issued new radiation-protection guidance, which has been approved by the President for all federal agencies.[7] This new guidance clearly adopts the ICRP methodology, and for the ingestion of radionuclides, exactly the same basic set of numerical guides are adopted. The federal guidance does state that these basic values ". . . do not apply to workers responsible for the management of or response to emergencies." An additional statement is made concerning emergency exposures:

> The numerical values recommended herein should not be deliberately exceeded except during emergencies, or under unusual circumstances for which the Federal agency having jurisdiction has carefully considered the reasons for doing so in light of these recommendations. If Federal agencies authorize dose equivalents greater than these values for unusual circumstances, they should make any generic procedures specifying conditions under which such exposures may occur publicly available or make specific instances in which such authorization has been given a matter of public record.

In order to implement the ICRP methodology for setting limits on the ingestion of radionuclides, the EPA has published its own compendium of exposure-to-dose factors and ALIs.[35] As these calculations have been done by the same people who were responsible for implementing the ICRP methodology, the numbers published by the EPA[35]

are the same as those published by the ICRP.[36] When initially published, the EPA numbers contained revisions that had not yet been published by the ICRP, but that has been rectified with the publication of ICRP Publication 30, Part 4.

The proposed revisions[8] of the NRC regulations also contain the same basic limits and methods of the ICRP.

MODIFICATION OF THE ICRP STRATEGY FOR ARMY FIELD-WATER-QUALITY STANDARDS

The goal of the Army in developing standards for field-water quality is clearly stated to be to limit the degradation of personnel performance under emergency field conditions (e.g., nuclear warfare). Additional specific instructions were to not consider stochastic effects. Thus, both the basic limits of the ICRP and the methodology of calculating ALIs must be modified to eliminate the consideration of effective dose equivalent.

Primary Limits for Committed Dose Equivalent

With the goal of protecting against significant performance degradation, we suggest a limit of 1.0 Sv (100 rem) committed dose equivalent to an individual organ or tissue of the GI tract as the basic standard. This should carry essentially zero risk of acute lethality.[a] Based upon the data in Fig. 3, no more than 10% of the affected troops should suffer performance degradation.[b]

Under extreme emergency conditions, this limit might be increased to as much as 2.0 Sv (200 rem).[a] Under conditions of protracted exposure (the curve to the right in Fig. 2), this should still result in zero incidence of lethalities, but might result in significant performance degradation (Fig. 3, see also Figs. 4 and 5).

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[a] If additional exposure is occurring via the route of external exposure and the inhalation of radionuclides, such exposure must be considered as part of the total exposure discussed here.

[b] The assumption is being made that a committed dose equivalent to an organ or tissue of the GI tract has the same effect as a dose to the whole body. This assumption is considered to be conservative, but it is not verified.

Limits for Intake and Concentration in Water

Ref. 35 contains a lengthy list of annual limits of intake (ALI) for radionuclides as calculated with the ICRP methodology, and it also contains a lengthy list of exposure-to-dose conversion factors. Most of the ALIs tabulated there, however, result from the limit on committed effective dose equivalent; thus, they cannot simply be multiplied by some factor to account for a different primary limit on committed dose equivalent to an individual organ or tissue of the GI tract. We have used the basic data on exposure-to-dose conversion factors, along with the primary limit on committed dose equivalent of 1.0 Sv (100 rem) to the GI tract, to derive new ALIs. These new values of ALI are listed for 727 radionuclides in Table A-1 of the Appendix.

The method used was to extract from Table 2.2 in Ref. 35 the exposure-to-dose conversion factors for the "remainder" organs. (Remainder in this table is the sum of the committed dose equivalent to the 5 organs not otherwise listed with the highest committed dose equivalents.) In cases where the dose to the "remainder" was actually dose limiting within the normal ICRP context, the organ responsible was also listed in Table 2.2 along with the organ specific exposure-to-dose conversion factor; the latter value was also extracted. In most cases, the "remainder" organs responsible were the stomach wall or the lower large intestinal wall. If the exposure-to-dose conversion value was available for more than one of these three organs, the maximum value was chosen.

The ALI for a radionuclide was then calculated by dividing 1.0 Sv by this maximum exposure-to-dose conversion value. The results are given in the Appendix both in terms of MBq and in μCi. The exposure-to-dose conversion factors for organs other than those of the GI tract were not used in deriving the new ALIs. However, if another organ did have a higher exposure-to-dose conversion factor, such values were extracted from Table 2.2. These values were then used to calculate the ratio by which the dose to this organ would be higher than the dose to an organ of the GI tract. These ratios are also given in Table A-1 of the Appendix, and the organ receiving the highest dose is indicated. The organs of interest are the thyroid (Thy), bone surface (B surf), red marrow (R marr), and the kidney (Kid). For example, for ^{129}I, it is noted that the dose to the thyroid would be 10,000 times higher than the dose to an organ of the GI tract. This would not cause performance degradation over the short term, but it may have long-term biological effects. It should also be noted that only radiological effects have been considered in these derivations, as is the case with the calculations contained in Ref. 35; the chemical effects of some compounds of some elements, notably uranium and beryllium, may be greater than the radiation effects.

Once the ALI is known, the limits in water are simply calculated by dividing by the expected amount of water to be consumed over the relevant time period. The four cases of interest are 5 and 15 L/d over 7 d (35 and 105 L, respectively) and 5 and 15 L/d over 365 d (1825 and 5475 L, respectively).

If more than one radionuclide is present, then fractions of ALIs should be calculated for each radionuclide and summed. This sum should not exceed 1. Allowance should also be made for dose received by any other pathway.

Under field conditions, it is not likely that sophisticated measurements can be made to identify individual radionuclides. Thus, some simpler approximations are needed. In order to accomplish this, the values for the individual radionuclides in Table A-1 of the Appendix were examined with the goal of deriving a more general standard for gross beta or alpha activity. The ALIs for the 727 radionuclides listed in Appendix Table A-1 vary from a minimum of .07 MBq to a maximum of 300,000 MBq. The arithmetic mean and standard deviation are 5700 and 20,000 MBq, respectively. The geometric mean and standard deviation are 830 MBq and 10, respectively; and the median is 1000 MBq. With such an extreme dispersion of values, the choice of some reference value for the general case of unidentified or gross alpha or beta activity is subjective. The minimum value of .07 MBq would be too conservative, while the arithmetic or geometric means would not offer protection against many radionuclides. To assist in choosing a reference value, the 727 radionuclides were sorted according to the ascending order of their ALIs. Those radionuclides that have ALIs of 40 MBq or less are listed in Table A-2 of the Appendix; also listed are some additional data on the type of radionuclide and their decay mode. From Table A-2, it is noted that only 37 radionuclides have ALIs less than 10 MBq, and most of these are transuranic radionuclides not likely to be encountered. Thus, we recommend the value of 10 MBq as the ALI to be used to protect against unidentified individual or gross alpha or gross beta activity.

Once the ALI for a particular radionuclide is known, or the value of 10 MBq for unidentified or gross activity is chosen, the limiting concentration in water is easily determined. The recommended procedures and values are summarized in Table 5.

As discussed above, the ingestion of some radionuclides in water at the recommended standards would result in committed dose equivalents to some organs that would be much larger than the committed dose equivalents to the organs of the GI tract. Thus, while performance would not be degraded over the short term, significant stochastic and non-stochastic biological effects might be expected over the long term. Those radionuclides for which this might be a special consideration are indicated in

Table 5. Recommended standards for radionuclides in military field-water supplies. These are intended only for emergency use to protect against performance degradation during a 7-day or 1-year period. The suggested values should not be applied to civilian populations or to peacetime military populations. The recommended standards are based upon a limit of 1.0 Sv (100 rem) to the organs of the GI tract. These values should be appropriately reduced, if exposure via other pathways is also occurring.

Time period	Water-consumption rate	
	5 L/d	15 L/d
For known individual radionuclides[a]:		
Long term (<1 y)	ALI/1825 L	ALI/5475 L
Short term (<7 d)	ALI/35 L	ALI/105 L
For gross beta and/or gross alpha activity:		
Long term (<1 y)	0.1 μCi/L (5 kBq/L)	0.05 μCi/L (2 kBq/L)
Short term (<7 d)	8 μCi/L (300 kBq/L)	3 μCi/L (100 kBq/L)

[a]The ALI is the annual limit of intake. Values for individual radionuclides are tabulated in Table A-1 the Appendix.

Table A-3 of the Appendix. Listed there are all of the radionuclides that would be expected to result in a committed dose equivalent of 5 times or more in some other organ as compared to the organs of the GI tract. It is noted that the organs of special interest are the bone surface and the thyroid. It has been noted by the ICRP[25] that adult mature cartilage will tolerate without necrosis as much as 70 Gy (7000 rad) fractionated over 10–12 weeks. Thus, the radionuclides ^{231}Pa, ^{232}Th, ^{123}Te, ^{229}Th, ^{230}Th, ^{41}Ca, ^{236}Np, and ^{237}Np deserve special consideration, but none appear to be likely sources of actual contamination at levels near the suggested standards. For the thyroid, the ICRP[25] indicates that the threshold for severe functional damage is approximately 25 to 30 Gy (2500 to 3000 rad) fractionated over 30 days. In consideration of long-term damage to the thyroid, then, special consideration might be given to the radionuclides ^{129}I, ^{125}I, ^{126}I, ^{131}I, ^{124}I, ^{133}I, ^{123}I, ^{130}I, ^{135}I, ^{132m}I, ^{121}I, and ^{132}Te. Fortunately, the uptake of any of these radionuclides by the thyroid could be blocked by the addition of iodine tablets to the water.

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Appendix: Values of Annual Limits on Intake (ALI)

Table A–1. A list of suggested values of annual limit on intake (ALI) for use by the Army under emergency conditions to protect against performance degradation during a 7-day or 1-year period. Also shown for reference are the ALIs recommended by the ICRP for the protection of occupational workers against the stochastic and non-stochastic effects of radiation. The "Army" values are based upon a limit of 1.0 Sv (100 rem) for the organs of the gastrointestinal (GI) tract. As indicated in the last two columns, some other organs may be committed to receiving very much higher doses; in some cases this would be expected to lead to serious damage occurring later in time. The suggested ALIs are only appropriate for emergency conditions, and should not be applied to civilian populations or to peacetime military populations.

Table A–2. A list of those radionuclides from Table A–1 with ALIs of 40 MBq or less. The type of the radionuclide is noted in Column 2: T=transuranic radionuclide; N=naturally occurring radionuclide; TD=daughter radionuclide of a transuranic radionuclide; and F=fission product. The decay mode is indicated in Column 3: SF=spontaneous fission; A=alpha particle emission; DA=daughter product decays by alpha particle emission; and DSF=daughter product decays by spontaneous fission.

Table A–3. An ordered list of those radionuclides from Table A–1 that would have a dose of 5 times higher or more in an organ other than those associated with the GI tract. The type of the radionuclide is noted in Column 2: T=transuranic radionuclide; N=naturally occurring radionuclide; TD=daughter radionuclide of a transuranic radionuclide; F=fission product; and UD=daughter radionuclide of U–233. The decay mode is indicated in Column 3: SF=spontaneous fission; A=alpha particle emission; DA=daughter product decays by alpha particle emission; and DSF=daughter product decays by spontaneous fission.

Table A-1. A list of suggested values of annual limit on intake (ALI) for use by the Army under emergency conditions to protect against performance degradation during a 7-day or 1-year period. Also shown for reference are the ALIs recommended by the ICRP for the protection of occupational workers against the stochastic and non-stochastic effects of radiation. The "Army" values are based upon a limit of 1.0 Sv (100 rem) for the organs of the gastrointestinal (GI) tract. As indicated in the last two columns, some other organs may be committed to receiving very much higher doses; in some cases this would be expected to lead to serious damage occurring later in time. The suggested ALIs are only appropriate for emergency conditions, and should not be applied to civilian populations or to peacetime military populations.

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
H-3	3E+03	6E+04	2E+06	1	
Be-7	1E+03	2E+04	5E+05	1	
Be-10	4E+01	8E+01	2E+03	1	
C-11	2E+04	3E+05	8E+06	1	
C-14	9E+01	2E+03	5E+04	1	
F-18	2E+03	3E+03	9E+04	1	
Na-22	2E+01	3E+02	8E+03	2	B surf
Na-24	1E+02	2E+03	5E+04	1	
Mg-28	2E+01	2E+02	5E+03	1	
Al-26	1E+01	1E+02	3E+03	1	
Si-31	3E+02	2E+03	6E+04	1	
Si-32	8E+01	2E+02	4E+03	1	
P-32	2E+01	4E+02	1E+04	3	R marr
P-33	2E+02	3E+03	8E+04	4	B surf
S-35	2E+02	4E+02	1E+04	1	
Cl-36	6E+01	1E+03	3E+04	1	
Cl-38	6E+02	1E+03	3E+04	1	
Cl-39	8E+02	2E+03	4E+04	1	
K-40	1E+01	2E+02	5E+03	1	
K-42	2E+02	2E+03	5E+04	1	
K-43	2E+02	3E+03	9E+04	1	
K-44	8E+02	2E+03	4E+04	1	
K-45	1E+03	2E+03	6E+04	1	
Ca-41	1E+02	4E+04	1E+06	100	B surf
Ca-45	6E+01	1E+03	3E+04	6	B surf
Ca-47	3E+01	2E+02	7E+03	1	
Sc-43	2E+02	2E+03	5E+04	1	
Sc-44	1E+02	9E+02	3E+04	1	
Sc-44m	2E+01	1E+02	4E+03	1	
Sc-46	3E+01	3E+02	7E+03	1	
Sc-47	8E+01	2E+02	4E+03	1	
Sc-48	3E+01	2E+02	6E+03	1	
Sc-49	7E+02	4E+03	1E+05	1	
Ti-44	8E+00	8E+01	2E+03	1	
Ti-45	3E+02	2E+03	6E+04	1	

Table A-1. (continued)

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
V-47	1E+03	2E+03	6E+04	1	
V-48	2E+01	2E+02	5E+03	1	
V-49	3E+03	5E+03	1E+05	1	
Cr-48	2E+02	2E+03	6E+04	1	
Cr-49	1E+03	7E+03	2E+05	1	
Cr-51	1E+03	1E+04	3E+05	1	
Mn-51	7E+02	4E+03	1E+05	1	
Mn-52	2E+01	3E+02	7E+03	1	
Mn-52m	1E+03	2E+03	5E+04	1	
Mn-53	2E+03	2E+04	4E+05	4	B surf
Mn-54	7E+01	8E+02	2E+04	1	
Mn-56	2E+02	1E+03	3E+04	1	
Fe-52	3E+01	2E+02	6E+03	1	
Fe-55	3E+02	3E+03	9E+04	1	
Fe-59	3E+01	3E+02	8E+03	1	
Fe-60	1E+00	2E+01	4E+02	1	
Co-55	4E+01	3E+02	9E+03	1	
Co-56	1E+01	2E+02	5E+03	1	
Co-57	2E+02	2E+03	5E+04	1	
Co-58	5E+01	6E+02	2E+04	1	
Co-58m	2E+03	1E+04	4E+05	1	
Co-60	7E+00	9E+01	3E+03	1	
Co-60m	4E+04	7E+04	2E+06	1	
Co-61	7E+02	4E+03	1E+05	1	
Co-62m	1E+03	3E+03	8E+04	1	
Ni-56	5E+01	5E+02	1E+04	1	
Ni-57	5E+01	4E+02	1E+04	1	
Ni-59	9E+02	1E+04	3E+05	1	
Ni-63	3E+02	3E+03	8E+04	1	
Ni-65	3E+02	2E+03	5E+04	1	
Ni-66	1E+01	3E+01	8E+02	1	
Cu-60	1E+03	2E+03	5E+04	1	
Cu-61	4E+02	3E+03	8E+04	1	
Cu-64	4E+02	3E+03	8E+04	1	
Cu-67	1E+02	1E+03	3E+04	1	
Zn-62	5E+01	4E+02	1E+04	1	
Zn-63	8E+02	2E+03	5E+04	1	
Zn-65	1E+01	2E+02	6E+03	1	
Zn-69	2E+03	1E+04	3E+05	1	
Zn-69m	1E+02	1E+03	3E+04	1	
Zn-71m	2E+02	2E+03	4E+04	1	
Zn-72	3E+01	3E+02	8E+03	1	
Ga-65	2E+03	3E+03	9E+04	1	
Ga-66	4E+01	3E+02	7E+03	1	

Table A-1. (continued)

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
Ga-67	2E+02	2E+03	5E+04	1	
Ga-68	5E+02	3E+03	9E+04	1	
Ga-70	2E+03	4E+03	1E+05	1	
Ga-72	4E+01	3E+02	8E+03	1	
Ga-73	2E+02	1E+03	3E+04	1	
Ge-66	9E+02	9E+03	3E+05	1	
Ge-67	1E+03	2E+03	5E+04	1	
Ge-68	2E+02	2E+03	6E+04	1	
Ge-69	5E+02	6E+03	2E+05	1	
Ge-71	2E+04	2E+05	6E+06	1	
Ge-75	2E+03	3E+03	8E+04	1	
Ge-77	3E+02	3E+03	8E+04	1	
Ge-78	7E+02	2E+03	5E+04	1	
As-69	1E+03	2E+03	6E+04	1	
As-70	4E+02	3E+03	8E+04	1	
As-71	1E+02	1E+03	3E+04	1	
As-72	3E+01	2E+02	6E+03	1	
As-73	3E+02	2E+03	5E+04	1	
As-74	5E+01	4E+02	1E+04	1	
As-76	4E+01	2E+02	6E+03	1	
As-77	1E+02	3E+02	8E+03	1	
As-78	3E+02	2E+03	5E+04	1	
Se-70	4E+02	3E+03	7E+04	1	
Se-73	1E+02	8E+02	2E+04	1	
Se-73m	1E+03	8E+03	2E+05	1	
Se-75	2E+01	2E+02	6E+03	1	
Se-79	2E+01	2E+02	5E+03	1	
Se-81	2E+03	5E+03	1E+05	1	
Se-81m	9E+02	5E+03	1E+05	1	
Se-83	1E+03	1E+04	3E+05	1	
Br-74	8E+02	2E+03	4E+04	1	
Br-74m	5E+02	1E+03	3E+04	1	
Br-75	1E+03	2E+03	5E+04	1	
Br-76	1E+02	2E+03	5E+04	1	
Br-77	6E+02	1E+04	3E+05	1	
Br-80	2E+03	4E+03	1E+05	1	
Br-80m	7E+02	6E+03	2E+05	1	
Br-82	1E+02	2E+03	5E+04	1	
Br-83	2E+03	3E+03	9E+04	1	
Br-84	7E+02	1E+03	4E+04	1	
Rb-79	1E+03	3E+03	7E+04	1	
Rb-81	1E+03	1E+04	3E+05	1	
Rb-81m	8E+03	2E+04	5E+05	1	
Rb-82m	4E+02	5E+03	1E+05	1	

Table A-1. (continued)

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
Rb-83	2E+01	5E+02	1E+04	1	
Rb-84	2E+01	4E+02	1E+04	2	B surf
Rb-86	2E+01	4E+02	1E+04	3	B surf
Rb-87	4E+01	9E+02	2E+04	3	B surf
Rb-88	7E+02	1E+03	4E+04	1	
Rb-89	1E+03	3E+03	7E+04	1	
Sr-80	1E+02	9E+02	3E+04	1	
Sr-81	8E+02	5E+03	1E+05	1	
Sr-82	7E+00	1E+01	4E+02	1	
Sr-83	7E+01	6E+02	2E+04	1	
Sr-85	9E+01	1E+03	4E+04	1	
Sr-85m	8E+03	7E+04	2E+06	1	
Sr-87m	1E+03	1E+04	3E+05	1	
Sr-89	2E+01	3E+01	9E+02	1	
Sr-90	1E+00	1E+02	4E+03	60	B surf
Sr-91	6E+01	4E+02	1E+04	1	
Sr-92	9E+01	6E+02	2E+04	1	
Y-86	4E+01	4E+02	1E+04	1	
Y-86m	8E+02	7E+03	2E+05	1	
Y-87	8E+01	7E+02	2E+04	1	
Y-88	3E+01	4E+02	9E+03	1	
Y-90	2E+01	3E+01	9E+02	1	
Y-90m	3E+02	2E+03	5E+04	1	
Y-91	2E+01	3E+01	9E+02	1	
Y-91m	4E+03	3E+04	9E+05	1	
Y-92	1E+02	6E+02	2E+04	1	
Y-93	4E+01	2E+02	7E+03	1	
Y-94	8E+02	2E+03	4E+04	1	
Y-95	1E+03	3E+03	7E+04	1	
Zr-86	5E+01	4E+02	1E+04	1	
Zr-88	1E+02	1E+03	3E+04	1	
Zr-89	5E+01	5E+02	1E+04	1	
Zr-93	5E+01	4E+03	1E+05	30	B surf
Zr-95	5E+01	4E+02	1E+04	1	
Zr-97	2E+01	1E+02	4E+03	1	
Nb-88	2E+03	3E+03	9E+04	1	
Nb-89	2E+02	1E+03	3E+04	1	
Nb-90	3E+01	3E+02	8E+03	1	
Nb-93m	3E+02	7E+02	2E+04	1	
Nb-94	3E+01	2E+02	6E+03	1	
Nb-95	7E+01	7E+02	2E+04	1	
Nb-95m	8E+01	2E+02	4E+03	1	
Nb-96	4E+01	3E+02	9E+03	1	
Nb-97	8E+02	5E+03	1E+05	1	

Table A-1. (continued)

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
Nb-98	5E+02	3E+03	9E+04	1	
Mo-90	7E+01	6E+02	2E+04	1	
Mo-93	1E+02	1E+03	3E+04	1	
Mo-93m	2E+02	1E+03	4E+04	1	
Mo-99	4E+01	7E+01	2E+03	1	
Mo-101	2E+03	3E+03	8E+04	1	
Tc-93	1E+03	1E+04	3E+05	1	
Tc-93m	3E+03	2E+04	6E+05	1	
Tc-94	3E+02	3E+03	9E+04	2	Thy
Tc-94m	7E+02	5E+03	1E+05	1	
Tc-95	4E+02	5E+03	1E+05	2	Thy
Tc-95m	1E+02	1E+03	4E+04	1	
Tc-96	7E+01	8E+02	2E+04	1	
Tc-96m	6E+03	6E+04	2E+06	1	
Tc-97	1E+03	9E+03	3E+05	2	Thy
Tc-97m	1E+02	1E+03	3E+04	2	Thy
Tc-98	4E+01	4E+02	1E+04	1	
Tc-99	1E+02	1E+03	3E+04	2	Thy
Tc-99m	3E+03	3E+04	8E+05	3	Thy
Tc-101	3E+03	7E+03	2E+05	1	
Tc-104	8E+02	2E+03	4E+04	1	
Ru-94	5E+02	4E+03	1E+05	1	
Ru-97	3E+02	3E+03	7E+04	1	
Ru-103	6E+01	5E+02	1E+04	1	
Ru-105	2E+02	1E+03	3E+04	1	
Ru-106	7E+00	1E+01	4E+02	1	
Rh-99	8E+01	8E+02	2E+04	1	
Rh-99m	6E+02	6E+03	2E+05	1	
Rh-100	6E+01	6E+02	2E+04	1	
Rh-101	8E+01	9E+02	2E+04	1	
Rh-101m	2E+02	2E+03	5E+04	1	
Rh-102	2E+01	2E+02	6E+03	1	
Rh-102m	4E+01	1E+02	3E+03	1	
Rh-103m	2E+04	1E+05	3E+06	1	
Rh-105	1E+02	3E+02	7E+03	1	
Rh-106m	3E+02	2E+03	6E+04	1	
Rh-107	3E+03	5E+03	1E+05	1	
Pd-100	4E+01	4E+02	1E+04	1	
Pd-101	4E+02	4E+03	1E+05	1	
Pd-103	2E+02	4E+02	1E+04	1	
Pd-107	1E+03	2E+03	6E+04	1	
Pd-109	9E+01	5E+02	1E+04	1	
Ag-102	2E+03	3E+03	9E+04	1	
Ag-103	1E+03	9E+03	2E+05	1	

Table A-1. (continued)

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
Ag-104	8E+02	7E+03	2E+05	1	
Ag-104m	1E+03	8E+03	2E+05	1	
Ag-105	9E+01	9E+02	2E+04	1	
Ag-106	2E+03	4E+03	1E+05	1	
Ag-106m	3E+01	3E+02	9E+03	1	
Ag-108m	2E+01	2E+02	6E+03	1	
Ag-110m	2E+01	2E+02	4E+03	1	
Ag-111	3E+01	7E+01	2E+03	1	
Ag-112	1E+02	7E+02	2E+04	1	
Ag-115	1E+03	2E+03	7E+04	1	
Cd-104	8E+02	7E+03	2E+05	1	
Cd-107	7E+02	5E+03	1E+05	1	
Cd-109	1E+01	9E+01	2E+03	4	Kidney
Cd-113	8E-01	7E+00	2E+02	4	Kidney
Cd-113m	9E-01	7E+00	2E+02	4	Kidney
Cd-115	3E+01	7E+01	2E+03	1	
Cd-115m	1E+01	7E+01	2E+03	1	
Cd-117	2E+02	1E+03	3E+04	1	
Cd-117m	2E+02	1E+03	3E+04	1	
In-109	7E+02	6E+03	2E+05	1	
In-110	2E+02	2E+03	5E+04	1	
In-111	1E+02	1E+03	3E+04	1	
In-112	6E+03	1E+04	3E+05	1	
In-113m	2E+03	1E+04	3E+05	1	
In-114m	1E+01	2E+01	6E+02	1	
In-115	1E+00	2E+01	4E+02	2	R marr
In-115m	5E+02	3E+03	9E+04	1	
In-116m	8E+02	6E+03	2E+05	1	
In-117	2E+03	1E+04	4E+05	1	
In-117m	4E+02	3E+03	7E+04	1	
In-119m	1E+03	3E+03	7E+04	1	
Sn-110	1E+02	9E+02	2E+04	1	
Sn-111	3E+03	2E+04	5E+05	1	
Sn-113	6E+01	1E+02	3E+03	1	
Sn-117m	6E+01	1E+02	3E+03	1	
Sn-119m	1E+02	2E+02	7E+03	1	
Sn-121	2E+02	4E+02	1E+04	1	
Sn-121m	1E+02	2E+02	6E+03	1	
Sn-123	2E+01	4E+01	1E+03	1	
Sn-123m	2E+03	1E+04	3E+05	1	
Sn-125	1E+01	3E+01	7E+02	1	
Sn-126	9E+00	8E+01	2E+03	1	
Sn-127	2E+02	2E+03	4E+04	1	
Sn-128	3E+02	2E+03	6E+04	1	

Table A-1. (continued)

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
Sb-115	3E+03	2E+04	5E+05	1	
Sb-116	3E+03	5E+03	1E+05	1	
Sb-116m	7E+02	6E+03	2E+05	1	
Sb-117	2E+03	2E+04	5E+05	1	
Sb-118m	2E+02	2E+03	5E+04	1	
Sb-119	5E+02	4E+03	1E+05	1	
Sb-120	3E+01	3E+02	9E+03	1	
Sb-122	3E+01	5E+01	1E+03	1	
Sb-124	2E+01	1E+02	4E+03	1	
Sb-124m	8E+03	2E+04	5E+05	1	
Sb-125	7E+01	5E+02	1E+04	1	
Sb-126	2E+01	1E+02	4E+03	1	
Sb-126m	2E+03	4E+03	1E+05	1	
Sb-127	3E+01	5E+01	1E+03	1	
Sb-128	4E+01	6E+03	2E+05	1	
Sb-129	1E+02	7E+02	2E+04	1	
Sb-130	6E+02	4E+03	1E+05	1	
Sb-131	6E+02	6E+03	2E+05	5	Thy
Te-116	3E+02	2E+03	5E+04	1	
Te-121	1E+02	1E+03	4E+04	1	
Te-121m	2E+01	6E+02	2E+04	20	B surf
Te-123	2E+01	3E+04	7E+05	800	B surf
Te-123m	2E+01	7E+02	2E+04	20	B surf
Te-125m	4E+01	7E+02	2E+04	9	B surf
Te-127	3E+02	2E+03	4E+04	1	
Te-127m	2E+01	3E+02	9E+03	7	B surf
Te-129	9E+02	6E+03	2E+05	1	
Te-129m	2E+01	1E+02	4E+03	1	
Te-131	1E+02	3E+03	7E+04	10	Thy
Te-131m	1E+01	3E+02	9E+03	10	Thy
Te-132	8E+00	7E+02	2E+04	40	Thy
Te-133	5E+02	2E+04	4E+05	20	Thy
Te-133m	1E+02	3E+03	9E+04	10	Thy
Te-134	6E+02	1E+04	3E+05	9	Thy
I-120	1E+02	3E+03	9E+04	10	Thy
I-120m	4E+02	4E+03	1E+05	5	Thy
I-121	4E+02	3E+04	9E+05	40	Thy
I-123	1E+02	5E+04	1E+06	200	Thy
I-124	2E+00	5E+03	1E+05	1000	Thy
I-125	1E+00	2E+04	5E+05	6000	Thy
I-126	8E-01	5E+03	1E+05	3000	Thy
I-128	2E+03	3E+03	8E+04	1	
I-129	2E-01	5E+03	1E+05	10000	Thy
I-130	1E+01	5E+03	1E+05	200	Thy

Table A-1. (continued)

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
I-131	1E+00	6E+03	2E+05	3000	Thy
I-132	1E+02	6E+03	2E+05	20	Thy
I-132m	1E+02	1E+04	4E+05	50	Thy
I-133	5E+00	6E+03	2E+05	600	Thy
I-134	8E+02	7E+03	2E+05	5	Thy
I-135	3E+01	6E+03	2E+05	100	Thy
Cs-125	2E+03	4E+03	1E+05	1	
Cs-127	2E+03	3E+04	7E+05	1	
Cs-129	8E+02	1E+04	4E+05	1	
Cs-130	2E+03	5E+03	1E+05	1	
Cs-131	7E+02	2E+04	4E+05	1	
Cs-132	1E+02	2E+03	5E+04	1	
Cs-134	3E+00	5E+01	1E+03	1	
Cs-134m	4E+03	9E+03	2E+05	1	
Cs-135	3E+01	5E+02	1E+04	1	
Cs-135m	3E+03	3E+04	7E+05	1	
Cs-136	2E+01	3E+02	8E+03	1	
Cs-137	4E+00	7E+01	2E+03	1	
Cs-138	7E+02	1E+03	4E+04	1	
Ba-126	2E+02	1E+03	4E+04	1	
Ba-128	2E+01	1E+02	3E+03	1	
Ba-131	1E+02	9E+02	2E+04	1	
Ba-131m	1E+04	3E+04	7E+05	1	
Ba-133	5E+01	7E+02	2E+04	1	
Ba-133m	9E+01	2E+02	5E+03	1	
Ba-135m	1E+02	7E+02	2E+04	1	
Ba-139	5E+02	3E+03	8E+04	1	
Ba-140	2E+01	4E+01	1E+03	1	
Ba-141	9E+02	5E+03	1E+05	1	
Ba-142	2E+03	1E+04	3E+05	1	
La-131	2E+03	1E+04	3E+05	1	
La-132	1E+02	8E+02	2E+04	1	
La-135	1E+03	1E+04	3E+05	1	
La-137	4E+02	4E+03	1E+05	1	
La-138	3E+01	3E+02	9E+03	1	
La-140	2E+01	2E+02	4E+03	1	
La-141	1E+02	8E+02	2E+04	1	
La-142	3E+02	2E+03	5E+04	1	
La-143	1E+03	3E+03	7E+04	1	
Ce-134	2E+01	4E+01	1E+03	1	
Ce-135	5E+01	4E+02	1E+04	1	
Ce-137	2E+03	1E+04	4E+05	1	
Ce-137m	8E+01	2E+02	5E+03	1	
Ce-139	2E+02	1E+03	4E+04	1	

Table A-1. (continued)

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
Ce-141	6E+01	1E+02	3E+03	1	
Ce-143	4E+01	9E+01	2E+03	1	
Ce-144	8E+00	2E+01	4E+02	1	
Pr-136	2E+03	4E+03	1E+05	1	
Pr-137	1E+03	9E+03	2E+05	1	
Pr-138m	4E+02	3E+03	8E+04	1	
Pr-139	1E+03	1E+04	3E+05	1	
Pr-142	4E+01	2E+02	6E+03	1	
Pr-142m	3E+03	2E+04	4E+05	1	
Pr-143	3E+01	7E+01	2E+03	1	
Pr-144	1E+03	2E+03	7E+04	1	
Pr-145	1E+02	7E+02	2E+04	1	
Pr-147	2E+03	4E+03	1E+05	1	
Nd-136	5E+02	4E+03	1E+05	1	
Nd-138	7E+01	5E+02	1E+04	1	
Nd-139	3E+03	2E+04	6E+05	1	
Nd-139m	2E+02	1E+03	4E+04	1	
Nd-141	5E+03	4E+04	1E+06	1	
Nd-147	4E+01	8E+01	2E+03	1	
Nd-149	4E+02	2E+03	7E+04	1	
Nd-151	2E+03	1E+04	4E+05	1	
Pm-141	2E+03	4E+03	1E+05	1	
Pm-143	2E+02	2E+03	5E+04	1	
Pm-144	4E+01	5E+02	1E+04	1	
Pm-145	4E+02	3E+03	9E+04	1	
Pm-146	5E+01	4E+02	1E+04	1	
Pm-147	2E+02	3E+02	9E+03	1	
Pm-148	2E+01	3E+01	9E+02	1	
Pm-148m	2E+01	2E+02	6E+03	1	
Pm-149	4E+01	9E+01	2E+03	1	
Pm-150	2E+02	1E+03	3E+04	1	
Pm-151	6E+01	4E+02	1E+04	1	
Sm-141	2E+03	3E+03	9E+04	1	
Sm-141m	9E+02	6E+03	2E+05	1	
Sm-142	3E+02	2E+03	5E+04	1	
Sm-145	2E+02	2E+03	4E+04	1	
Sm-146	5E-01	2E+01	5E+02	20	B surf
Sm-147	6E-01	2E+01	5E+02	20	B surf
Sm-151	5E+02	1E+03	3E+04	1	
Sm-153	6E+01	1E+02	3E+03	1	
Sm-155	2E+03	4E+03	1E+05	1	
Sm-156	2E+02	1E+03	3E+04	1	
Eu-145	5E+01	6E+02	2E+04	1	
Eu-146	3E+01	3E+02	9E+03	1	

Table A-1. (continued)

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
Eu-147	9E+01	8E+02	2E+04	1	
Eu-148	3E+01	4E+02	1E+04	1	
Eu-149	4E+02	3E+03	9E+04	1	
Eu-150	3E+01	3E+02	8E+03	1	
Eu-152	3E+01	3E+02	7E+03	1	
Eu-152m	9E+01	6E+02	2E+04	1	
Eu-154	2E+01	2E+02	4E+03	1	
Eu-155	1E+02	9E+02	2E+04	1	
Eu-156	2E+01	1E+02	4E+03	1	
Eu-157	8E+01	5E+02	1E+04	1	
Eu-158	6E+02	4E+03	1E+05	1	
Gd-145	1E+03	3E+03	9E+04	1	
Gd-146	4E+01	4E+02	1E+04	1	
Gd-147	7E+01	6E+02	2E+04	1	
Gd-148	5E-01	2E+01	5E+02	20	B surf
Gd-149	9E+01	8E+02	2E+04	1	
Gd-151	2E+02	2E+03	4E+04	1	
Gd-152	6E-01	3E+01	7E+02	20	B surf
Gd-153	2E+02	1E+03	3E+04	1	
Gd-159	9E+01	6E+02	2E+04	1	
Tb-147	3E+02	2E+03	6E+04	1	
Tb-149	2E+02	1E+03	4E+04	1	
Tb-150	2E+02	1E+03	3E+04	1	
Tb-151	1E+02	1E+03	3E+04	1	
Tb-153	2E+02	1E+03	4E+04	1	
Tb-154	6E+01	6E+02	2E+04	1	
Tb-155	2E+02	2E+03	4E+04	1	
Tb-156	4E+01	3E+02	9E+03	1	
Tb-156m	2E+02	2E+03	6E+04	1	
Tb-157	6E+02	1E+03	3E+04	1	
Tb-158	4E+01	4E+02	1E+04	1	
Tb-160	3E+01	2E+02	6E+03	1	
Tb-161	6E+01	1E+02	3E+03	1	
Dy-155	3E+02	3E+03	8E+04	1	
Dy-157	7E+02	6E+03	2E+05	1	
Dy-159	4E+02	3E+03	9E+04	1	
Dy-165	5E+02	3E+03	8E+04	1	
Dy-166	2E+01	4E+01	1E+03	1	
Ho-155	1E+03	1E+04	3E+05	1	
Ho-157	9E+02	7E+04	2E+06	1	
Ho-159	7E+03	5E+04	1E+06	1	
Ho-161	4E+03	3E+04	7E+05	1	
Ho-162	2E+04	4E+04	1E+06	1	
Ho-162m	2E+03	1E+04	4E+05	1	

Table A-1. (continued)

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
Ho-164	7E+03	1E+04	4E+05	1	
Ho-164m	3E+03	2E+04	6E+05	1	
Ho-166	3E+01	7E+01	2E+03	1	
Ho-166m	2E+01	2E+02	6E+03	1	
Ho-167	6E+02	4E+03	1E+05	1	
Er-161	5E+02	5E+03	1E+05	1	
Er-165	2E+03	2E+04	5E+05	1	
Er-169	1E+02	2E+02	6E+03	1	
Er-171	1E+02	8E+02	2E+04	1	
Er-172	4E+01	9E+01	2E+03	1	
Tm-162	2E+03	5E+03	1E+05	1	
Tm-166	1E+02	1E+03	4E+04	1	
Tm-167	8E+01	2E+02	4E+03	1	
Tm-170	3E+01	6E+01	2E+03	1	
Tm-171	4E+02	8E+02	2E+04	1	
Tm-172	3E+01	5E+01	1E+03	1	
Tm-173	1E+02	1E+03	3E+04	1	
Tm-175	3E+03	5E+03	1E+05	1	
Yb-162	2E+03	2E+04	5E+05	1	
Yb-166	4E+01	4E+02	1E+04	1	
Yb-167	1E+04	7E+04	2E+06	1	
Yb-169	6E+01	5E+02	1E+04	1	
Yb-175	1E+02	2E+02	5E+03	1	
Yb-177	6E+02	4E+03	1E+05	1	
Yb-178	5E+02	3E+03	8E+04	1	
Lu-169	9E+01	8E+02	2E+04	1	
Lu-170	4E+01	4E+02	1E+04	1	
Lu-171	6E+01	5E+02	1E+04	1	
Lu-172	3E+01	3E+02	8E+03	1	
Lu-173	2E+02	1E+03	4E+04	1	
Lu-174	2E+02	1E+03	3E+04	1	
Lu-174m	8E+01	2E+02	4E+03	1	
Lu-176	3E+01	2E+02	6E+03	1	
Lu-176m	3E+02	2E+03	5E+04	1	
Lu-177	8E+01	2E+02	4E+03	1	
Lu-177m	3E+01	2E+02	5E+03	1	
Lu-178	1E+03	3E+03	7E+04	1	
Lu-178m	2E+03	4E+03	1E+05	1	
Lu-179	2E+02	1E+03	4E+04	1	
Hf-170	9E+01	8E+02	2E+04	1	
Hf-172	4E+01	4E+02	1E+04	2	B surf
Hf-173	2E+02	2E+03	4E+04	1	
Hf-175	1E+02	9E+02	2E+04	1	
Hf-177m	7E+02	5E+03	1E+05	1	

Table A-1. (continued)

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
Hf-178m	9E+00	1E+02	4E+03	1	B surf
Hf-179m	3E+01	3E+02	7E+03	1	
Hf-180m	3E+02	2E+03	6E+04	1	
Hf-181	4E+01	3E+02	8E+03	1	
Hf-182	7E+00	4E+02	1E+04	30	B surf
Hf-182m	1E+03	9E+03	2E+05	1	
Hf-183	7E+02	5E+03	1E+05	1	
Hf-184	9E+01	6E+02	2E+04	1	
Ta-172	1E+03	8E+03	2E+05	1	
Ta-173	2E+02	2E+03	4E+04	1	
Ta-174	9E+02	6E+03	2E+05	1	
Ta-175	2E+02	2E+03	5E+04	1	
Ta-176	1E+02	1E+03	3E+04	1	
Ta-177	4E+02	3E+03	8E+04	1	
Ta-178	6E+02	5E+03	1E+05	1	
Ta-179	7E+02	6E+03	1E+05	1	
Ta-180	5E+01	4E+02	1E+04	1	
Ta-180m	8E+02	6E+03	2E+05	1	
Ta-182	3E+01	2E+02	6E+03	1	
Ta-182m	6E+03	1E+04	3E+05	1	
Ta-183	3E+01	7E+01	2E+03	1	
Ta-184	7E+01	5E+02	1E+04	1	
Ta-185	9E+02	6E+03	2E+05	1	
Ta-186	2E+03	4E+03	1E+05	1	
W-176	4E+02	3E+03	9E+04	1	
W-177	7E+02	6E+03	2E+05	1	
W-178	2E+02	1E+03	4E+04	1	
W-179	2E+04	1E+05	3E+06	1	
W-181	5E+02	4E+03	1E+05	1	
W-185	8E+01	2E+02	4E+03	1	
W-187	7E+01	5E+02	1E+04	1	
W-188	1E+01	3E+01	8E+02	1	
Re-177	3E+03	7E+03	2E+05	1	
Re-178	3E+03	5E+03	1E+05	1	
Re-181	2E+02	2E+03	5E+04	3	Thy
Re-182	5E+01	5E+02	1E+04	2	Thy
Re-184	8E+01	9E+02	2E+04	1	
Re-184m	6E+01	5E+02	1E+04	1	
Re-186	6E+01	5E+02	1E+04	2	Thy
Re-186m	5E+01	9E+01	3E+03	1	
Re-187	2E+04	2E+05	4E+06	2	Thy
Re-188	6E+01	5E+02	1E+04	3	Thy
Re-188m	3E+03	2E+04	6E+05	3	Thy
Re-189	1E+02	9E+02	2E+04	3	Thy

Table A–1. (continued)

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro–Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
Os–180	4E+03	3E+04	7E+05	1	
Os–181	5E+02	4E+03	1E+05	1	
Os–182	8E+01	7E+02	2E+04	1	
Os–185	8E+01	9E+02	2E+04	1	
Os–189m	3E+03	2E+04	4E+05	1	
Os–191	8E+01	2E+02	4E+03	1	
Os–191m	5E+02	3E+03	8E+04	1	
Os–193	6E+01	1E+02	3E+03	1	
Os–194	2E+01	3E+01	9E+02	1	
Ir–182	1E+03	3E+03	8E+04	1	
Ir–184	3E+02	2E+03	6E+04	1	
Ir–185	2E+02	1E+03	3E+04	1	
Ir–186	9E+01	8E+02	2E+04	1	
Ir–187	4E+02	3E+03	8E+04	1	
Ir–188	6E+01	6E+02	2E+04	1	
Ir–189	2E+02	4E+02	1E+04	1	
Ir–190	3E+01	3E+02	8E+03	1	
Ir–190m	6E+03	5E+04	1E+06	1	
Ir–192	3E+01	2E+02	7E+03	1	
Ir–192m	1E+02	1E+03	3E+04	1	
Ir–194	3E+01	2E+02	6E+03	1	
Ir–194m	2E+01	2E+02	5E+03	1	
Ir–195	5E+02	3E+03	9E+04	1	
Ir–195m	3E+02	2E+03	5E+04	1	
Pt–186	5E+02	4E+03	1E+05	1	
Pt–188	6E+01	5E+02	1E+04	1	
Pt–189	3E+02	3E+03	8E+04	1	
Pt–191	1E+02	1E+03	3E+04	1	
Pt–193	1E+03	3E+03	8E+04	1	
Pt–193m	9E+01	2E+02	5E+03	1	
Pt–195m	7E+01	1E+02	4E+03	1	
Pt–197	1E+02	7E+02	2E+04	1	
Pt–197m	6E+02	4E+03	1E+05	1	
Pt–199	2E+03	1E+04	3E+05	1	
Pt–200	4E+01	2E+02	6E+03	1	
Au–193	3E+02	2E+03	6E+04	1	
Au–194	1E+02	1E+03	3E+04	1	
Au–195	2E+02	1E+03	3E+04	1	
Au–198	4E+01	3E+02	8E+03	1	
Au–198m	3E+01	2E+02	7E+03	1	
Au–199	1E+02	2E+02	6E+03	1	
Au–200	9E+02	6E+03	2E+05	1	
Au–200m	4E+01	3E+02	9E+03	1	
Au–201	3E+03	5E+03	1E+05	1	

Table A-1. (continued)

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
Hg-193	5E+02	4E+03	1E+05	1	
Hg-193m	1E+02	8E+02	2E+04	1	
Hg-194	6E-01	7E+00	2E+02	1	
Hg-195	5E+02	3E+03	9E+04	1	
Hg-195m	8E+01	5E+02	1E+04	1	
Hg-197	2E+02	1E+03	4E+04	1	
Hg-197m	1E+02	6E+02	2E+04	1	
Hg-199m	E+03	5E+03	1E+05	1	
Hg-203	2E+01	1E+02	4E+03	1	
Tl-194	8E+03	2E+04	5E+05	1	
Tl-194m	2E+03	4E+03	1E+05	1	
Tl-195	2E+03	2E+04	5E+05	1	
Tl-197	3E+03	3E+04	7E+05	1	
Tl-198	7E+02	8E+03	2E+05	1	
Tl-198m	1E+03	1E+04	3E+05	1	
Tl-199	2E+03	2E+04	6E+05	1	
Tl-200	3E+02	4E+03	1E+05	1	
Tl-201	6E+02	8E+03	2E+05	1	
Tl-202	1E+02	2E+03	5E+04	1	
Tl-204	6E+01	7E+02	2E+04	1	
b-195m	2E+03	1E+04	4E+05	1	
Pb-198	1E+03	9E+03	3E+05	1	
Pb-199	8E+02	7E+03	2E+05	1	
Pb-200	1E+02	9E+02	3E+04	1	
Pb-201	3E+02	2E+03	6E+04	1	
Pb-202	5E+00	1E+02	3E+03	1	
Pb-202m	3E+02	3E+03	8E+04	1	
Pb-203	2E+02	2E+03	4E+04	1	
Pb-205	1E+02	3E+03	7E+04	10	B surf
Pb-209	9E+02	5E+03	1E+05	1	
Pb-210	2E-02	5E-01	1E+01	10	B surf
Pb-211	4E+02	2E+03	7E+04	1	
Pb-212	3E+00	7E+01	2E+03	10	B surf
Pb-214	3E+02	3E+03	8E+04	1	
Bi-200	1E+03	8E+03	2E+05	1	
Bi-201	4E+02	3E+03	8E+04	1	
Bi-202	5E+02	4E+03	1E+05	1	
Bi-203	9E+01	8E+02	2E+04	1	
Bi-205	5E+01	5E+02	1E+04	1	
Bi-206	2E+01	2E+02	6E+03	1	
Bi-207	3E+01	3E+02	8E+03	1	
Bi-210	3E+01	2E+02	5E+03	1	
Bi-210m	2E+00	1E+01	3E+02	4	Kid
Bi-212	2E+02	1E+03	3E+04	1	

Table A-1. (continued)

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
Bi-213	3E+02	2E+03	4E+04	1	
Bi-214	6E+02	1E+03	3E+04	1	
Po-203	9E+02	8E+03	2E+05	1	
Po-205	8E+02	7E+03	2E+05	1	
Po-207	3E+02	3E+03	7E+04	1	
Po-210	1E-01	7E-01	2E+01	1	
At-207	2E+02	4E+03	9E+04	1	
At-211	5E+00	9E+01	2E+03	1	
Fr-222	8E+01	1E+03	3E+04	1	
Fr-223	2E+01	4E+02	1E+04	1	
Ra-223	2E-01	9E+00	2E+02	30	B surf
Ra-224	3E-01	1E+01	4E+02	20	B surf
Ra-225	3E-01	2E+01	7E+02	40	B surf
Ra-226	7E-02	1E+01	3E+02	70	B surf
Ra-227	6E+02	1E+04	3E+05	9	B surf
Ra-228	9E-02	6E+00	2E+02	40	B surf
Ac-224	6E+01	1E+02	4E+03	1	
Ac-225	2E+00	4E+00	1E+02	1	
Ac-226	4E+00	9E+00	2E+02	1	
Ac-227	7E-03	3E-01	9E+00	20	B surf
Ac-228	9E+01	7E+02	2E+04	2	B surf
Th-226	2E+02	4E+02	1E+04	1	
Th-227	5E+00	4E+01	1E+03	3	B surf
Th-228	2E-01	3E+01	7E+02	60	B surf
Th-229	2E-02	4E+01	1E+03	800	B surf
Th-230	1E-01	6E+01	2E+03	200	B surf
Th-231	1E+02	8E+02	2E+04	1	
Th-232	3E-02	7E+01	2E+03	1000	B surf
Th-234	1E+01	2E+01	6E+02	1	
Pa-227	1E+02	8E+02	2E+04	1	
Pa-228	4E+01	5E+02	1E+04	5	B surf
Pa-230	2E+01	4E+02	1E+04	9	B surf
Pa-231	7E-03	6E+01	2E+03	4000	B surf
Pa-232	5E+01	5E+02	1E+04	3	B surf
Pa-233	5E+01	1E+02	3E+03	1	
Pa-234	9E+01	6E+02	2E+04	1	
U-230	1E-01	3E+00	8E+01	10	B surf
U-231	2E+02	3E+02	9E+03	1	
U-232	8E-02	3E+00	8E+01	20	B surf
U-233	4E-01	9E+00	2E+02	10	B surf
U-234	4E-01	9E+00	2E+02	10	B surf
U-235	5E-01	1E+01	3E+02	10	B surf
U-236	5E-01	1E+01	3E+02	10	B surf
U-237	6E+01	1E+02	3E+03	1	

Table A-1. (continued)

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
U-238	5E-01	1E+01	3E+02	10	B surf
U-239	2E+03	1E+04	4E+05	1	
U-240	4E+01	3E+02	7E+03	1	
Np-232	5E+03	5E+04	1E+06	3	B surf
Np-233	3E+04	2E+05	5E+06	1	
Np-234	7E+01	6E+02	2E+04	1	
Np-235	8E+02	2E+03	4E+04	1	
Np-236	9E-02	3E+01	7E+02	100	B surf
Np-237	2E-02	5E+00	1E+02	100	B surf
Np-238	5E+01	3E+02	9E+03	1	
Np-239	6E+01	1E+02	3E+03	1	
Np-240	8E+02	5E+03	1E+05	1	
Pu-234	3E+02	2E+03	6E+04	1	
Pu-235	3E+04	2E+05	5E+06	1	
Pu-236	9E-02	4E+00	1E+02	20	B surf
Pu-237	4E+02	3E+03	8E+04	1	
Pu-238	3E-02	2E+00	5E+01	30	B surf
Pu-239	3E-02	2E+00	4E+01	30	B surf
Pu-240	3E-02	2E+00	4E+01	30	B surf
Pu-241	1E+00	9E+01	2E+03	30	B surf
Pu-242	3E-02	2E+00	4E+01	30	B surf
Pu-243	6E+02	3E+03	9E+04	1	
Pu-244	3E-02	2E+00	4E+01	30	B surf
Pu-245	7E+01	4E+02	1E+04	1	
Pu-246	1E+01	3E+01	7E+02	1	
Am-237	3E+03	2E+04	6E+05	1	
Am-238	1E+03	1E+04	3E+05	1	
Am-239	2E+02	1E+03	3E+04	1	
Am-240	7E+01	6E+02	2E+04	1	
Am-241	3E-02	2E+00	4E+01	30	B surf
Am-242m	3E-02	2E+00	4E+01	30	B surf
Am-242	1E+02	1E+03	3E+04	1	
Am-243	3E-02	2E+00	4E+01	30	B surf
Am-244m	2E+03	4E+03	1E+05	1	
Am-244	9E+01	7E+02	2E+04	1	
Am-245	1E+03	6E+03	2E+05	1	
Am-246m	2E+03	4E+03	1E+05	1	
Am-246	1E+03	7E+03	2E+05	1	
Cm-238	5E+02	4E+03	1E+05	1	
Cm-240	2E+00	4E+01	1E+03	8	B surf
Cm-241	4E+01	4E+02	1E+04	2	B surf
Cm-242	1E+00	2E+01	7E+02	10	B surf
Cm-243	4E-02	2E+00	5E+01	20	B surf
Cm-244	5E-02	2E+00	7E+01	20	B surf

Table A-1. (continued)

Radionuclide	ICRP ALI (MBq)	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
Cm-245	3E-02	1E+00	4E+01	30	B surf
Cm-246	3E-02	1E+00	4E+01	30	B surf
Cm-247	3E-02	2E+00	4E+01	30	B surf
Cm-248	7E-03	4E-01	1E+01	30	B surf
Cm-249	2E+03	1E+04	3E+05	1	
Cm-250	1E-03	7E-02	2E+00	30	B surf
Bk-245	8E+01	5E+02	1E+04	1	
Bk-246	9E+01	8E+02	2E+04	1	
Bk-247	2E-02	3E+00	7E+01	70	B surf
Bk-249	7E+00	7E+02	2E+04	50	B surf
Bk-250	3E+02	2E+03	7E+04	1	
Cf-244	9E+02	2E+03	5E+04	1	
Cf-246	1E+01	9E+01	2E+03	1	
Cf-248	3E-01	2E+01	5E+02	40	B surf
Cf-249	2E-02	3E+00	7E+01	70	B surf
Cf-250	4E-02	5E+00	1E+02	60	B surf
Cf-251	2E-02	2E+00	7E+01	70	B surf
Cf-252	9E-02	6E+00	2E+02	40	B surf
Cf-253	7E+00	3E+02	8E+03	20	B surf
Cf-254	8E-02	9E-01	3E+01	6	B surf
Es-250	2E+03	2E+04	5E+05	4	B surf
Es-251	3E+02	2E+03	5E+04	1	
Es-253	5E+00	5E+01	1E+03	4	B surf
Es-254m	1E+01	2E+01	6E+02	1	
Es-254	3E-01	2E+01	5E+02	30	B surf
Fm-252	2E+01	1E+02	3E+03	1	
Fm-253	4E+01	3E+02	9E+03	4	B surf
Fm-254	1E+02	7E+02	2E+04	1	
Fm-255	2E+01	1E+02	3E+03	1	
Fm-257	7E-01	3E+01	8E+02	20	B surf
Md-257	3E+02	3E+03	7E+04	4	B surf
Md-258	9E-01	3E+01	9E+02	20	B surf

Table A-2. A list of those radionuclides from Table A-1 with ALIs of 40 MBq or less. The type of the radionuclide is noted in Column 2: T=transuranic radionuclide; N=naturally occurring radionuclide; TD=daughter radionuclide of a transuranic radionuclide; and F=fission product. The decay mode is indicated in Column 3: SF=spontaneous fission; A=alpha particle emission; DA=daughter product decays by alpha particle emission; and DSF=daughter product decays by spontaneous fission.

Radionuclide	Type	Decay mode	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
Cm-250	T	SF	7E-02	2E+00	30	B surf
Ac-227	N	A	3E-01	9E+00	20	B surf
Cm-248	T	A	4E-01	1E+01	30	B surf
Pb-210	N	A	5E-01	1E+01	10	B surf
Po-210	N	A	7E-01	2E+01	1	
Cf-254	T	A	9E-01	3E+01	6	B surf
Cm-245	T	A	1E+00	4E+01	30	B surf
Cm-246	T	A	1E+00	4E+01	30	B surf
Am-241	T	A	2E+00	4E+01	30	B surf
Am-243	T	A	2E+00	4E+01	30	B surf
Pu-240	T	A	2E+00	4E+01	30	B surf
Pu-239	T	A	2E+00	4E+01	30	B surf
Cm-247	T	A	2E+00	4E+01	30	B surf
Am-242m	T	A	2E+00	4E+01	30	B surf
Pu-244	T	A	2E+00	4E+01	30	B surf
Pu-242	T	A	2E+00	4E+01	30	B surf
Pu-238	T	A	2E+00	5E+01	30	B surf
Cm-243	T	A	2E+00	5E+01	20	B surf
Cm-244	T	A	2E+00	7E+01	20	B surf
Cf-251	T	A	2E+00	7E+01	70	B surf
Cf-249	T	A	3E+00	7E+01	70	B surf
Bk-247	T	A	3E+00	7E+01	70	B surf
U-230	TD	A	3E+00	8E+01	10	B surf
U-232	TD	A	3E+00	8E+01	20	B surf
Ac-225		A	4E+00	1E+02	1	
Pu-236	T	A,SF	4E+00	1E+02	20	B surf
Cf-250	T	A	5E+00	1E+02	60	B surf
Np-237	T	A	5E+00	1E+02	100	B surf
Ra-228	N	A	6E+00	2E+02	40	B surf
Cf-252	T	A	6E+00	2E+02	40	B surf
Hg-194			7E+00	2E+02	1	
Cd-113	F		7E+00	2E+02	4	Kidney
Cd-113m	F		7E+00	2E+02	4	Kidney
Ra-223	N	A	9E+00	2E+02	30	B surf
Ac-226		DA	9E+00	2E+02	1	
U-233		A	9E+00	2E+02	10	B surf
U-234	N	A	9E+00	2E+02	10	B surf
Ra-226	N	A	1E+01	3E+02	70	B surf
U-236	TD	A	1E+01	3E+02	10	B surf

Table A-2. (continued)

Radionuclide	Type	Decay mode	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
U-235	N	A	1E+01	3E+02	10	B surf
U-238	N	A	1E+01	3E+02	10	B surf
Bi-210m		A	1E+01	3E+02	4	Kid
Ra-224	N	A	1E+01	4E+02	20	B surf
Sr-82			1E+01	4E+02	1	
Ru-106	F		1E+01	4E+02	1	
Ce-144	F		2E+01	4E+02	1	
In-115	F		2E+01	4E+02	2	R marr
Fe-60			2E+01	4E+02	1	
Sm-146		A	2E+01	5E+02	20	B surf
Es-254	T	A	2E+01	5E+02	30	B surf
Sm-147	F	A	2E+01	5E+02	20	B surf
Cf-248	T	A	2E+01	5E+02	40	B surf
Gd-148		A	2E+01	5E+02	20	B surf
Es-254m	T	DA	2E+01	6E+02	1	
In-114m			2E+01	6E+02	1	
Th-234	N	DA	2E+01	6E+02	1	
Ra-225		DA	2E+01	7E+02	40	B surf
Cm-242	T	A	2E+01	7E+02	10	B surf
Th-228	N	A	3E+01	7E+02	60	B surf
Pu-246	T	DA	3E+01	7E+02	1	
Sn-125	F		3E+01	7E+02	1	
Np-236	T	DSF	3E+01	7E+02	100	B surf
Gd-152	N	A	3E+01	7E+02	20	B surf
Fm-257	T	A	3E+01	8E+02	20	B surf
Ni-66			3E+01	8E+02	1	
W-188			3E+01	8E+02	1	
Md-258	T	A	3E+01	9E+02	20	B surf
Y-90	F		3E+01	9E+02	1	
Pm-148	F		3E+01	9E+02	1	
Os-194			3E+01	9E+02	1	
Y-91	F		3E+01	9E+02	1	
Sr-89	F		3E+01	9E+02	1	
Th-229	UD	A	4E+01	1E+03	800	B surf
Ce-134			4E+01	1E+03	1	
Cm-240	T		4E+01	1E+03	8	B surf
Ba-140	F		4E+01	1E+03	1	
Sn-123	F		4E+01	1E+03	1	
Th-227	N	A	4E+01	1E+03	3	B surf
Dy-166	F		4E+01	1E+03	1	

Table A-3. An ordered list of those radionuclides from Table A-1 that would have a dose of 5 times higher or more in an organ other than those associated with the GI tract. The type of the radionuclide is noted in Column 2: T=transuranic radionuclide; N=naturally occurring radionuclide; TD=daughter radionuclide of a transuranic radionuclide; F=fission product; and UD=daughter radionuclide of U-233. The decay mode is indicated in Column 3: SF=spontaneous fission; A=alpha particle emission; DA=daughter product decays by alpha particle emission; and DSF=daughter product decays by spontaneous fission.

Radionuclide	Type	Decay mode	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
I-129	F		5E+03	1E+05	10000	Thy
I-125			2E+04	5E+05	6000	Thy
Pa-231	N	A	6E+01	2E+03	4000	B surf
I-126			5E+03	1E+05	3000	Thy
I-131	F		6E+03	2E+05	3000	Thy
Th-232	N	A	7E+01	2E+03	1000	B surf
I-124			5E+03	1E+05	1000	Thy
Te-123	N		3E+04	7E+05	800	B surf
Th-229	UD	A	4E+01	1E+03	800	B surf
I-133	F		6E+03	2E+05	600	Thy
Th-230	N	A	6E+01	2E+03	200	B surf
I-123			5E+04	1E+06	200	Thy
I-130			5E+03	1E+05	200	Thy
Ca-41			4E+04	1E+06	100	B surf
Np-236	T	DSF	3E+01	7E+02	100	B surf
I-135	F		6E+03	2E+05	100	Thy
Np-237	T	A	5E+00	1E+02	100	B surf
Cf-249	T	A	3E+00	7E+01	70	B surf
Cf-251	T	A	2E+00	7E+01	70	B surf
Bk-247	T	A	3E+00	7E+01	70	B surf
Ra-226	N	A	1E+01	3E+02	70	B surf
Sr-90	F		1E+02	4E+03	60	B surf
Th-228	N	A	3E+01	7E+02	60	B surf
Cf-250	T	A	5E+00	1E+02	60	B surf
I-132m	F		1E+04	4E+05	50	Thy
Bk-249	T	SF	7E+02	2E+04	50	B surf
I-121			3E+04	9E+05	40	Thy
Cf-248	T	A	2E+01	5E+02	40	B surf
Cf-252	T	A	6E+00	2E+02	40	B surf
Ra-228	N	A	6E+00	2E+02	40	B surf
Ra-225		DA	2E+01	7E+02	40	B surf
Te-132	F		7E+02	2E+04	40	Thy
Am-242m	T	A	2E+00	4E+01	30	B surf
Hf-182			4E+02	1E+04	30	B surf
Am-243	T	A	2E+00	4E+01	30	B surf
Cm-246	T	A	1E+00	4E+01	30	B surf
Zr-93	F		4E+03	1E+05	30	B surf
Cm-245	T	A	1E+00	4E+01	30	B surf

Table A-3. (continued)

Radionuclide	Type	Decay mode	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
Ra-223	N	A	9E+00	2E+02	30	B surf
Pu-242	T	A	2E+00	4E+01	30	B surf
Cm-250	T	SF	7E-02	2E+00	30	B surf
Pu-240	T	A	2E+00	4E+01	30	B surf
Cm-248	T	A	4E-01	1E+01	30	B surf
Pu-238	T	A	2E+00	5E+01	30	B surf
Cm-247	T	A	2E+00	4E+01	30	B surf
Pu-241	T		9E+01	2E+03	30	B surf
Pu-244	T	A	2E+00	4E+01	30	B surf
Pu-239	T	A	2E+00	4E+01	30	B surf
Am-241	T	A	2E+00	4E+01	30	B surf
Es-254	T	A	2E+01	5E+02	30	B surf
Cf-253	T	DA	3E+02	8E+03	20	B surf
Cm-244	T	A	2E+00	7E+01	20	B surf
Cm-243	T	A	2E+00	5E+01	20	B surf
Gd-148		A	2E+01	5E+02	20	B surf
Ra-224	N	A	1E+01	4E+02	20	B surf
Md-258	T	A	3E+01	9E+02	20	B surf
Te-123m			7E+02	2E+04	20	B surf
I-132	F		6E+03	2E+05	20	Thy
Te-133	F		2E+04	4E+05	20	Thy
Te-121m			6E+02	2E+04	20	B surf
Gd-152	N	A	3E+01	7E+02	20	B surf
Pu-236	T	ASF	4E+00	1E+02	20	B surf
Sm-146		A	2E+01	5E+02	20	B surf
Sm-147	F	A	2E+01	5E+02	20	B surf
Fm-257	T	A	3E+01	8E+02	20	B surf
Ac-227	N	A	3E-01	9E+00	20	B surf
U-232	TD	A	3E+00	8E+01	20	B surf
U-238	N	A	1E+01	3E+02	10	B surf
U-236	TD	A	1E+01	3E+02	10	B surf
Pb-205			3E+03	7E+04	10	B surf
U-234	N	A	9E+00	2E+02	10	B surf
U-235	N	A	1E+01	3E+02	10	B surf
U-230		A	3E+00	8E+01	10	B surf
Cm-242	T	A	2E+01	7E+02	10	B surf
Pb-212	N	DA	7E+01	2E+03	10	B surf
I-120			3E+03	9E+04	10	Thy
Pb-210	N	A	5E-01	1E+01	10	B surf
Te-131	F		3E+03	7E+04	10	Thy
U-233		A	9E+00	2E+02	10	B surf
Te-131m	F		3E+02	9E+03	10	Thy
Te-133m	F		3E+03	9E+04	10	Thy
Pa-230	TD	DA	4E+02	1E+04	9	B surf

Table A-3. (continued)

Radionuclide	Type	Decay mode	Army ALI (MBq)	Army ALI (micro-Ci)	Ratio: Highest dose in other organ to dose in GI	Organ with highest dose
Te-134	F		1E+04	3E+05	9	Thy
Te-125m	F		7E+02	2E+04	9	B surf
Ra-227		DA	1E+04	3E+05	9	B surf
Cm-240	T	A	4E+01	1E+03	8	B surf
Te-127m	F		3E+02	9E+03	7	B surf
Ca-45			1E+03	3E+04	6	B surf
Cf-254	T	A	9E-01	3E+01	6	B surf
Hf-178m			1E+02	4E+03	6	B surf
Sb-131	F		6E+03	2E+05	5	Thy
Pa-228		A	5E+02	1E+04	5	B surf
I-120m			4E+03	1E+05	5	Thy
I-134	F		7E+03	2E+05	5	Thy

CHAPTER 4. ORGANOPHOSPHORUS NERVE AGENTS

J. I. Daniels*

INTRODUCTION

The OP compounds that are nerve agents possess properties that make them superior CW munitions for military forces. These properties include (1) relatively fast-acting acute toxicity, (2) effectiveness whether inhaled or absorbed through the skin, (3) ease of dispersal, (4) stability in storage, and (5) fairly low manufacturing costs.[1] The initial development of these compounds was conducted by I. G. Farbenindustrie in Germany just prior to and during the second World War.[2-4] Originally, these compounds were investigated for their suitability as insecticides, but the German government soon recognized the military applicability of chemicals with such potent toxicity and redirected the research to the use of these compounds in warfare.[1-4] From the time of this early work until the present, there have been four OP nerve agents that have received the greatest amount of consideration as threat agents:[1]

- Tabun (also known as agent GA), which is O-ethyl N-dimethylphosphoramidocyanidate,
- Sarin (also known as agent GB), which is O-isopropylmethylphosphonofluoridate,
- Soman (also known as agent GD), which is O-1,2,2-trimethylpropyl methylphosphonofluoridate, and
- Agent VX, which is O-ethyl S-[2-(diisopropylamino)ethyl]-methylphosphonothioate.

According to Meselson and Robinson,[1] tabun (GA), sarin (GB), and soman (GD) were first prepared in Germany between 1936 and 1944. These authors also state that the standard OP nerve-agent munitions stockpiled by the United States are sarin and VX, and

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that soman is believed to be the standard OP nerve agent in the arsenal of the Soviet Union. However, older quantities of tabun, the first of the OP nerve agents considered suitable for warfare, may also be part of the Soviet Union's current inventory of nerve-agent munitions.[1]

Meselson and Robinson explain that the method for release of the OP nerve agents in the battlefield depends on their volatility.[1] For example, sarin (GB), which is nearly as volatile as water, is most effective when released as an airborne contaminant to exert its toxicity after absorption through the lungs. On the other hand, VX possesses a volatility close to that of lubricating oil and is more suited for release as a contact agent, exerting its toxicity following skin absorption. The volatility of soman (GD) is between that for sarin and that for VX (at 25°C the volatilities for sarin, soman, and VX are 22,000; 3,900; and 10.5 mg/m^3, respectively),[5] but thickeners can be employed to reduce this volatility, presumably to one which is more like that of VX.[1,4] Thus, soman (GD) appears to have potential use as either an inhalation or contact poison. These OP compounds are very effective as threat agents, particularly when broadcast into the air or over the ground, because small quantities of these compounds can be lethal in a short period of time to populations of exposed military personnel.

The inhibition of the enzyme acetylcholinesterase (AChE) and the subsequent rapid accumulation of acetylcholine at cholinergic synapses (junctions between nerves or nerves and muscles in the tissues across which acetylcholine transmits the nerve impulse) is considered the principal mechanism by which the four OP nerve agents induce acute toxicity.[1,6] The enzyme AChE normally decomposes the acetylcholine to inactive components so that the properties of a cholinergic synapse can be restored to a rest condition to receive the next nerve-impulse transmission.[3] By inactivating this enzyme, the OP nerve agents promote effects equivalent to continuous excitation of the cholinergic nerve fibers.[4] Among the acute symptoms that can occur as a consequence of excessive accumulation of acetylcholine are uncontrollable vomiting and defecation, convulsions, loss of reflexes, coma, and central respiratory failure, which leads to death.[1,4]

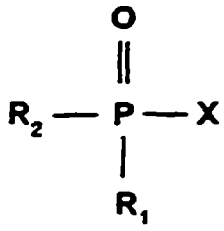
Even though the inhibition of AChE is widely accepted as the major toxic action of the OP threat agents of concern, these substances can apparently affect nerve-impulse transmission by more direct processes as well. Rickett et al.[7] review the studies that have shown unequivocally that these four OP threat agents can directly affect the receptor sites for acetylcholine in "excitable" tissue. For example, GA, GB, and GD were all found to be capable of changing receptor sites in a way somewhat similar to that produced by acetylcholine, which promotes the conductance of the electrophysiological signals associated with stimulation of neuromuscular function. The receptor sites are

changed differently by VX because this threat agent blocks signal conductance, even if acetylcholine is present at the receptor, thereby interrupting neuromuscular function. Significant implications of these observations are that the inhibition of AChE is only one indicator of the toxicity of the OP threat agents and these compounds actually produce toxic effects by their action at multiple sites. These discoveries concerning the physiological consequences of the nerve agents upon target organs are a direct result of modern technological advances (e.g., voltage and patch clamp techniques that measure ionic conductance in neurotransmitter systems) that were not available before the 1970's. Therefore, future studies using such technology should be performed to provide dose-response functions that improve upon the present understanding of the relationship between AChE inhibition and toxicity as described by empirical data. Until such data become available, the existing data, which focus on the relationship between AChE inhibition and toxicity, must continue to be relied upon to evaluate the possibility of adverse health effects developing in individuals exposed to OP threat agents and to derive the recommendations for interim field-water-quality standards for these compounds that are presented in this chapter.

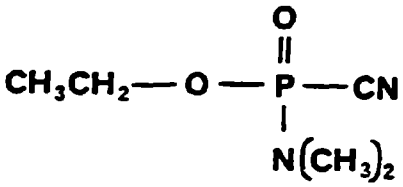
CHEMICAL PROPERTIES

The general chemical structure of OP compounds that inhibit AChE is presented in Fig. 1, along with the specific structure of each of the four OP threat agents of interest. The most acutely toxic OP compounds usually contain a carbon-phosphorus bond, a characteristic feature of all four OP threat agents.[4] Agent GA is a methylphosphor-amidocyanidic acid derivative; agents GB and GD are methylphosphonofluoridic acid derivatives; and Agent VX is a derivative of methylphosphonothioic acid.[8] Typically, the OP compounds that inhibit AChE are lipid-soluble and are rapidly and effectively absorbed following almost any route of administration.[4]

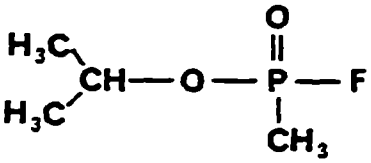
The inactivation of AChE by an OP threat agent presumably involves the nucleophilic attack on the phosphorous of the OP compound by an OH^- of the enzyme, and the subsequent production of a phosphorylated enzyme.[3,4] During the course of this reaction, the "leaving group" of the organophosphorus compound (see Fig. 1) departs and is replaced by AChE.[3] This chemical reaction occurs at the active site of the enzyme[3]; consequently, the AChE is prevented from reacting with its normal substrate, acetylcholine. The phosphorylated enzyme is a very stable molecule; natural hydrolytic regeneration of the active enzyme occurs at a slow or negligible rate, which accounts for



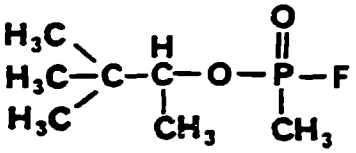
A. General structure of organophosphorus compounds that are cholinesterase inhibitors. Possible substituents of R_1 and R_2 include alkyl, alkoxy, aryloxy, amido, and mercapto groups. The X or "leaving group" may be either a halide, cyanide, thiocyanate, phenoxy, thiophenoxy, phosphate, alkylthioethylmercaptide, dialkylaminoethylmercaptide, or carboxylate group.



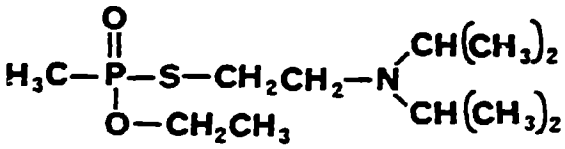
B. Tabun (agent GA), where cyanide is the leaving group.



C. Sarin (agent GB), where fluoride is the leaving group.



D. Soman (agent GD), where fluoride is the leaving group.



E. Agent VX, where dialkylaminoalkylmercaptide is the leaving group.

Figure 1. The general and specific chemical structures of the four OP threat agents of interest.[4,7,8]

the fact that the amount of inactivated AChE can increase with time under conditions of repeated exposure.[4] In fact, some OP compounds can rapidly make the phosphorylated enzyme completely resistant to spontaneous or pharmaceutically induced reactivation by splitting-off an additional alkyl or alkoxy group from the phosphorous on the inhibited enzyme. The result is an even more stable monoalkyl- or monoalkoxy-phosphoryl AChE.[4] According to Sidell and Groff,[9] this process depends on the size of the R_2 group attached to the phosphorus (see Fig. 1); larger structures are more effective in preventing reactivation of the AChE because they make it difficult for the phosphorous to be readily displaced from the enzyme by another neuclophile such as the OH^- of water. Usually this suppression of reactivation occurs within minutes or hours after the initial phosphorylation; this process is called "aging." Thus, it is not surprising that soman, which has the largest R_2 group of the four OP nerve agents of interest (see Fig. 1), produces the most rapidly aged enzyme.[4]

BEHAVIOR IN WATER

Among the four OP threat agents of military concern, the two most carefully studied with respect to their decomposition in water have been GB (O-isopropyl methylphosphonofluoridate, or sarin) and VX (O-ethyl S-[2-(diisopropylamino)ethyl]-methylphosphonothioate). Data are very limited regarding the behavior of GD (O-1,2,2-trimethylpropyl methylphosphonofluoridate, or soman) in water, and there is almost no detailed information available about the decomposition of GA (O-ethyl N-dimethylphosphoramidocyanidate, or tabun) in water, although hydrogen cyanide (HCN) is reported to be one of the hydrolysis products of GA.[5] Accordingly, the available information concerning the behavior of GB, VX, and GD in water are summarized next.

In a report describing the properties of GB in water, Epstein states that GB is very soluble and will dissolve rapidly.[10] Also mentioned in this report is that the decomposition of GB involves hydrolysis to two strong acids (isopropyl methylphosphonic acid and hydrofluoric acid) and that the rate of this hydrolysis will depend upon the temperature, pH, and type and concentration of the dissolved solids present in the water.

As explained by Epstein,[10] at elevated levels of pH (between 6.5 and 14) hydrolysis is mediated by hydroxide-ion attack and at low levels of pH (between 0 and 4) hydrolysis is speeded by hydronium-ion catalysis; however, the hydrolysis rate of GB is at a minimum at pH levels between 4 and 6.5 where the reaction is between GB and water molecules. Because of the effect of pH on hydrolysis, the hydrolysis of GB will be fastest when a

sufficiently high concentration of GB is introduced into an unbuffered or slightly buffered aqueous solution that is initially at a pH level of about 7. The reason for this is that under such conditions appreciable quantities of acid-hydrolysis products will form and depress the pH of the solution past the pH range where the rate of hydrolysis is slowest (4 to 6.5) and into the acid-catalysis pH range (0 to 4) where the rate of hydrolysis is most rapid. Demek et al.[11] added a concentrated GB solution to a sample of seawater and observed the hydrolysis to be slow at first, then to accelerate. They concluded that the slow and then fast rates of hydrolysis correspond to the passage of the pH of the solution through the region of maximum GB stability and into the pH range of faster, acid-catalyzed hydrolysis.

Increasing the temperature also will accelerate the hydrolysis process; however, the effect will be greater for hydrolysis under alkaline conditions than for hydrolysis under acidic conditions.[10] For example, for each 10°C rise in temperature the rate of hydrolysis will increase about fourfold for solutions in the pH range of alkaline hydrolysis. However, for solutions in the pH range of acid hydrolysis the rate of hydrolysis will increase only about twofold per 10°C rise in temperature.

Experimental evidence concerning the behavior of GB in seawater[11,12] indicates that in waters with neutral or slightly alkaline pH, the half-life of GB can be reduced dramatically by the presence of trace quantities of metal salts. For example, in seawater, the half-life of GB is approximately 30 min at 25°C and pH 7.9, but in distilled water at a pH of 8 and a temperature of 25°C, the half-life of GB is 7.5 h.[10,12] The accelerated hydrolysis of GB in seawater is attributed primarily to the presence of elevated concentrations of magnesium ion (Mg^{+2}). In fact, one experiment involving seawater at pH 7.2 and 24°C showed that when the concentration of Mg^{+2} was lowered by the addition of ethylenediaminetetraacetic acid (EDTA), the half-life of the GB in the water was extended (i.e., in the absence of EDTA, the half-life of GB was 2 h; after the maximum amount of EDTA was added, the half-life of GB was extended to about 18 h).[13] Although other metal compounds such as cupric ion can be even more effective catalysts for hydrolysis of GB, especially in freshwater, at the pH levels of most natural waters (i.e., pH $\geq$ 7) cupric ion and other metals are not likely to be in solution at concentrations high enough to be of practical significance.[10,11]

Data concerning the behavior of VX in seawater suggest that this threat agent may hydrolyze very slowly and therefore be more stable in seawater than GB.[11] For example, VX was shown to be very stable in seawater at pH 10 (half-life of 14 h), but under similar conditions GB was shown to hydrolyze rapidly (half-life of 10 s); the temperature at which these experiments were performed was not stated.[13] Additionally, metal ions present in

seawater are of little importance with regard to VX hydrolysis, but particles that are present can adsorb some VX, which might protect some of the compound from hydrolysis and inaccurately indicate a faster rate of disappearance of VX.[11]

Epstein et al.[14] examined the kinetics and mechanisms of hydrolysis of VX in dilute aqueous solutions. The results of this research indicate that the products of VX hydrolysis are dependent on the pH of the solution. For example, at pH levels greater than 10 and less than about 7, only the P-S bond is cleaved, and the resulting products are diisopropylaminoethyl mercaptan and ethyl methylphosphonic acid. At pH levels between about 7 and 10, VX undergoes three simultaneous reactions so that the P-S, C-O, and S-C bonds are cleaved, and additional products are formed, including bisdiisopropyl-aminoethylaminosulfide and S-diisopropylaminoethylmethylphosphonic acid. Small[15] transformed the hydrolysis rate constant data for VX versus pH at 25°C reported by Epstein et al.[14] into a figure showing the half-life of VX hydrolysis in water as a function of pH. The transformed data indicate that in dilute aqueous solution at a pH level of 6, the half-life of VX hydrolysis will exceed 1000 h; however, with increasing pH levels, the half-life of VX will decrease, so that at a pH level of 10, the half-life will be only tens of hours.

Data on the behavior of soman (GD) in water are very limited. For example, Broomfield et al.[16] recently found it necessary to study the stability of GD in aqueous solutions normally found under laboratory conditions because of a need for these data in studies of the toxicological and pharmacological properties of the compound. Their studies showed that at room temperature (21°C), the hydrolysis of 50% of a solution of 1 mM soman in 0.15 N sodium chloride, initially at a pH of 6.4, would take over 5 d to occur. Another result from this study showed that the rate of hydrolysis of higher concentrations of soman under similar conditions increased more rapidly as a consequence of the release of acidic hydrolysis products and the fact that hydrolysis is acid-catalyzed. Finally, they observed that the rate of hydrolysis of soman was markedly slower at lower temperatures. For example, 90% of the soman remained after 40 d when a solution of 1 mM soman in sodium chloride, initially at a pH of 6.4, was stored at a temperature of 1°C. Interestingly, these authors conclude that in the absence of contamination by soman-hydrolyzing enzymes like those present in rodents and rabbits, a solution of 1 mM soman in 0.15 N sodium chloride or water that is kept on ice in the laboratory would not degrade for several days. This suggests that soman may be more persistant in water supplies that are at lower temperatures. Like GB, a principal hydrolysis product of GD is reported to be hydrofluoric acid; however, the half-life of GD is longer (e.g., 45 h at a pH of 6.65 and a temperature of 25°C).[5]

On the basis of the previous discussion, it is evident that the rates of decomposition of an OP threat agent are agent-specific (e.g., ranging from seconds to hours or hours to days) and depend on the chemical and physical properties of the field water into which the agent has been introduced. Additionally, it is conceivable that stabilizers will be added to the agents to make them resist hydrolysis in munitions because it is not cost effective to produce munitions containing purified agent exclusively.[7,15] However, the toxicity of these stabilizers and whether or not they will interfere with hydrolysis of the agent in dilute aqueous solutions have not been well defined.

TOXICITY OF HYDROLYSIS PRODUCTS

According to Epstein,[12] rats given water containing up to 200 ppm of the hydrolysis products of GB for a 3-wk period showed no signs of illness. The data from this study suggest that the toxicity of the hydrolysis products of GB is negligible with respect to performance degradation in military personnel consuming field water over a 7-d period containing these products.

Data concerning the toxicity of the hydrolysis products of GA, or GD were not readily available. However, if decomposition does occur in a fashion similar to the hydrolysis of GB, there should be a loss of toxicity and reactivity of the hydrolysis products of these compounds. This is because the leaving group (see Fig. 1) is replaced by OH^-, which is not reactive with the AChE. Additionally, the anion of the OP threat agent that is produced by hydrolysis can resist the attack of the enzyme because of charge repulsion.[12]

The toxicology of the hydrolysis products of VX has not been studied in great detail. However, a report prepared by Small[17] contains a summary of toxicological data from selected references that includes some median lethal dose (LD50) data for laboratory animals for two of the hydrolysis products of VX that might occur in water that is at a pH between 7 and 10 (e.g., bisdiisopropylaminoethylaminosulfide and S-diisopropylamino-ethylmethylphosphonic acid). Although such data are limited, they suggest that hydrolysis of VX to these products does not necessarily mean that the water containing these products will be potable. Consequently, water that has been contaminated by VX should always undergo treatment prior to consumption by military personnel.

DETECTION IN WATER

The M272 Chemical Agents Water Testing Kit now being introduced by the U.S. Army is a new and improved version of the chemical agent detection kit that is part of the Water Quality Analysis Set.[18,19] The test for OP nerve agents in this kit involves a colorimetric comparison test based on the inhibition of eel cholinesterase enzyme. This particular method is capable of detecting concentrations as low as 1 μg/L of OP nerve agents. If an OP agent is present at or above the detection limit and reacts with the enzyme, there is no change in color of the white material on which the reaction takes place. If an OP agent is not present, or is present at a level below the detection limit (e.g., the field-water-quality standard), then the material on which the reaction takes place turns blue. Thus, the test is suitable for determining whether or not the OP threat agent is present at a concentration that is of military concern. Moreover, under the proper conditions a test using eel cholinesterase enzyme in combination with spectrophotometry can be made very sensitive and has been used to estimate concentrations of GB and VX in seawater at the parts-per-trillion (ng/L) level.[13]

PHARMACOKINETICS

The absorption, distribution, metabolism, and elimination of the OP compounds that can inactivate AChE have been reviewed in a report addressing the possible long-term health effects of short-term exposure to chemical agents. This report was prepared by the Committee on Toxicology of the National Research Council.[4] According to this report, the OP compounds likely to be found in military stockpiles are lipid-soluble, and this property accounts for their effective absorption by almost any route of exposure. Furthermore, once absorbed, these OP compounds or their metabolites can bind to proteins in the blood and tissues, which explains their ability to inhibit AChE activity. However, AChE-inhibiting OP compounds can also undergo hydrolysis by phosphorylphosphatase enzymes in the body, and the resulting metabolites will be excreted in urine. In fact, the report indicates that elimination of most OP compounds from human systems occurs almost exclusively by the process just described. Nevertheless, according to a review of data by McNamara et al.[20] there is no evidence to suggest that this mechanism plays a significant role in modifying the effects of acutely toxic concentrations of these compounds. Furthermore, there are no data available to indicate the degree to which straight aqueous hydrolysis in the body might contribute to the detoxification and elimination of OP agents.

HEALTH EFFECTS

As mentioned earlier, the inactivation of AChE at cholinergic synapses by an OP threat agent is generally considered the principal mechanism by which acute toxicity is induced in humans. Without the AChE to inactivate the neurotransmitter substance, acetylcholine, continuous stimulation of nerve fibers leads to the disruption of nerve and organ function. According to Grob and Harvey,[21] gastrointestinal effects, including anorexia, nausea, vomiting, abdominal cramps, diarrhea, and fecal incontinence, should be among the earliest symptoms following ingestion of an acutely toxic dose of an OP threat agent, either as the result of a single exposure or multiple exposures over a short time period. Moreover, these authors reported that the initial gastrointestinal effects may be followed by profuse sweating, dyspnea, and reduction in breathing capacity. They also explain that the initial signs and symptoms of acute toxicity depend on the route and degree of exposure. For example, sweating and sometimes muscular fasciculations are expected to occur first after percutaneous exposure, and respiratory effects, including chest tightening, wheezing, and dyspnea, are the immediate effects that can be anticipated after inhalation of an acutely toxic dose. Additionally, several reports[4,21,22] indicate that, generally, ocular effects such as miosis (pupillary constriction), a sensation of pressure within and behind the eye, and frontal headache are responses to localized ocular exposure. However, observations by Kimura et al.[23] from a study involving intravenous administration of VX to human volunteers indicate that frontal headaches may also result from systemic exposure to OP compounds.

Although the signs and symptoms of acute toxicity from OP threat agents appear to be correlated with inactivation of AChE in the synapses of the tissues, OP threat agents also react with the chemically similar AChE that is bound to the surface of red blood cells (RBC-ChE) and with a second cholinesterase known as pseudocholinesterase or butyrylcholinesterase (BuChE), which is present in blood plasma and some organs, such as the liver. Eto[24] describes the principal locations, biochemical properties, and nomenclature of these two cholinesterases in most mammals. The two types of cholinesterase are distinguished biochemically by their substrate specificity; AChE most rapidly hydrolyzes its natural substrate, acetylcholine, whereas BuChE will preferentially hydrolyze butyrylcholine and propionylcholine rather than acetylcholine.

The biological function of pseudocholinesterase has not been determined,[3,24,25] and apparently the enzyme can be totally inhibited without harmful consequences.[3] Wills[25] cites reports that indicate the AChE associated with red blood cells appears to do nothing more than contribute to the control of that cell's permeability. He concludes that both

RBC-ChE and BuChE probably exert a protective action with respect to functional AChE by reacting with an absorbed dose of a cholinesterase-inhibiting substance (e.g., an anticholinesterase chemical such as an OP threat agent or a related OP pesticide) before it reaches the functional AChE in the tissues. However, according to Wills,[25] the degree of such protection will vary, depending on the physical and chemical characteristics of the anticholinesterase chemical absorbed. Route of exposure and amount of exposure (e.g., chronic) might also affect the degree of protection.

Recently, researchers have started to study the effects of subacute exposure to OP threat agents and pesticides that may not be related directly to cholinesterase inactivation. These effects have been listed by Clement,[26] and some are discussed briefly in the report by the Committee on Toxicology of the National Research Council.[4] From the perspective of military performance, the most significant effects needing further study are behavioral effects, cardiac effects, tolerance to chronic exposure of sublethal doses, muscle necrosis, neuropathy, and effects resulting from interaction with enzymes other than the two types of cholinesterase (AChE of the tissue and red blood cell and BuChE of the plasma).

Neurotoxic esterase (NTE), one of the other enzymes inhibited by OP threat agents, has received considerable attention. This attention is associated with evidence that some OP compounds related to the threat agents can produce a delayed neuropathy in humans 8 to 14 d after exposure, and this neuropathy may be associated with inactivation of NTE.[27,28] For example, the experimental organisms (particularly the hen) that can be made to develop a delayed-neurotoxicity syndrome similar to that seen in humans exhibit a corresponding loss of NTE activity in their nervous system.[4,27-30] However, delayed neuropathy, which in humans involves weakness and ataxia in the lower limbs and, secondarily, degeneration of some nerve fibers, is species-, compound-, and dose-dependent.[27] The traditional animal test species for inducing a delayed neuropathy syndrome similar to that in humans have been the hen (the most frequently used experimental organism for studying this effect) and the cat.[27] However, Veronesi[31] has presented evidence indicating that the rat may also be an adequate animal model for delayed neurotoxicity because the neuropathological changes in rats caused by some OP compounds are similar to those characterizing delayed neuropathy in hens, cats, and humans. Nonetheless, experimental and clinical evidence indicates that survivable doses of OP threat agents will not produce delayed neuropathy in humans.[4,27-30] For example, studies with hens that have been protected by drugs so that they can survive the administration of lethal doses of GA, GB, and GD revealed that the dose of these compounds necessary to produce delayed neurotoxicity is far greater than that needed to

produce lethality.[27-29] Thus, further studies involving appropriate animal models are needed to determine if military personnel under battlefield conditions who are given drugs that will allow them to survive single or accumulated lethal doses of these threat agents would suffer from delayed neurotoxicity after such exposure. Additionally, the available data concerning delayed neurotoxicity indicate that this effect is not pertinent with respect to setting short-term standards for field water for the OP threat agents GA, GB, and GD.

Experimental evidence indicates that VX is a poor inhibitor of NTE, and that thioate compounds like VX are generally not neuropathic. Thus, delayed neurotoxicity is not considered to be a concern for drug-protected humans surviving doses of VX that are normally lethal.[27]

Finally, carcinogenic, mutagenic, and teratogenic effects are not generally associated with OP threat agents. In fact, the evidence from a study of the long-term health effects of anticholinesterase OP threat agents administered to military volunteers in tests conducted over 25 years ago supports this judgment.[4,32] Nevertheless, the study concludes that exposures to low doses of the OP threat agents may have produced subtle, persistent changes in the electroencephalogram (EEG), sleep rate, and behavior of these military volunteers. However, the authors of the study state that such changes would be difficult to detect without a new study comparing the current EEG, sleep rate, and behavior of the volunteers with those of a control group.[32]

DEVELOPMENT OF MAXIMUM PERMISSIBLE CONCENTRATIONS (MPCs) FOR CONSIDERATION AS INTERIM FIELD-WATER-QUALITY STANDARDS

As noted earlier, the development of maximum permissible concentrations (MPCs) for OP threat agents in field water for consideration as interim standards will be based on the relationship between AChE inhibition and toxicity as described by empirical data reported in the literature. This relationship is used because no other measurement is available for quantitatively linking the effects of sublethal doses of an OP threat agent, even after repetitive administration, with the potential for adverse health consequences in either humans or laboratory animals. However, there is evidence that other mechanisms besides inhibition of AChE by OP threat agents probably contribute to the production of toxic effects. Among these mechanisms are direct effects by OP threat agents on acetylcholine receptor sites.[7] Thus, inhibition of AChE by OP threat agents might not be the only important mechanism by which toxicity occurs. Nevertheless, the inhibition of

AChE by OP threat agents remains the only quantitative measurement reported in the literature to indicate at least the potential for toxicity to develop. Therefore, the relationship between AChE inhibition and toxicity is described next and those other mechanisms that might have an effect on the development of toxicity are also mentioned.

The observable signs and symptoms of acute intoxication produced by OP anticholinesterase compounds, particularly the OP threat agents, can be considered equivalent for a given route of exposure.[21,25,33] Also, evidence from studies involving laboratory animals, primarily rodents, indicates that low doses of OP threat agents can produce significant behavioral disturbances, which are detectable only by sensitive tests, without producing the overt symptoms characteristic of acute poisoning.[34,35] The OP threat agents that reach the central nervous system seem to produce such behavioral effects at remarkably lower doses than the OP threat agents that preferentially affect the peripheral nervous system. However, whether or not an OP compound can reach the central nervous system at all may depend on route of administration. For example, results of experiments performed by Sidell and Groff[9] involving VX administered intravenously and in drinking water to human volunteers suggest that VX, an OP threat agent that can act on the central nervous system, may not reach the central nervous system when administered orally to humans. Additionally, the inhibition by OP anticholinesterases of the AChE enzyme at the neuroeffector junctions (synapses) of target tissues appears to contribute significantly to the production of adverse health effects.[25,33]

Furthermore, adverse health effects are not expected to develop unless the absorbed dose of an OP anticholinesterase compound can depress the activity of AChE in the tissues below a critical level.[33] Grob and Harvey[22] indicate that 50% of the normal activity of the AChE of the tissues (50% depression) is estimated to be the threshold level below which changes in tissue function may begin to occur. Moreover, they report that 10 to 20% of the normal activity of the AChE of the tissues (80 to 90% depression) is estimated to be the level below which more serious or even fatal alterations of tissue function may occur. Sivam et al.[36] also showed that a substantial inhibition of AChE activity (over 90%) in brain tissue of rats by the OP threat agents GA, GB, and GD is associated with lethality. However, these researchers do conclude that other factors may also be involved directly or indirectly in the expression of lethality. In addition, Maxwell et al.[37] cite reports that reflect the disagreement that exists over the relative importance of the extent of cholinesterase inhibition in comparison to the rate at which that inhibition occurs with regard to the production of acute toxicity.

Even though acute toxicity from OP anticholinesterase compounds has been attributed, at least in part, to inactivation of the AChE of the tissues, monitoring of the

activity of this enzyme in the tissue in vivo is not possible. Consequently, the alternative to in vivo monitoring has been to determine the impact of these compounds on inactivation of the AChE bound to red blood cells.[21,33] In fact, Grob and Harvey[22] showed that the AChE of the red blood cell, muscle, and brain were equally sensitive in vitro to inactivation by the OP threat agent sarin (GB). They cited additional evidence from earlier post-mortem studies of humans that revealed that following oral exposure to OP anticholinesterase compounds, for short periods, the AChE enzyme of the brain and muscle tissues was depressed almost to the same degree as the AChE enzyme associated with red blood cells. Additionally, Sim and Stubbs[38] concluded from a review of the responses of military personnel who volunteered to receive a single percutaneous dose of the OP threat agent, VX, that a correlation exists between the depression of RBC-ChE below 50% of normal activity and the first appearance of any observable signs and symptoms (e.g., headaches) of potential significance. Data presented by Kimura et al.[23] from experiments involving intravenous administration of VX to human volunteers also suggest that observable symptoms of potential significance will not occur until RBC-ChE activity is depressed below 50% of normal. Based on the information just presented, we assume that a single dose of an OP threat agent, by any route of exposure, that is sufficient to depress the AChE activity of the red blood cells rapidly to levels equal to or less than 50% of normal activity will produce a virtually identical effect on the activity of the functional AChE at the neuroeffector junctions of the tissues. This effect on AChE activity in the tissues is reported by Grob and Harvey[22] to be associated with the first appearance of observable alteration of tissue function.

The assumption just made for the case of a single dose of an OP threat agent and its corresponding functional significance can be considered a conservative one (i.e., the RBC-ChE is probably inactivated to a greater extent than the functional AChE of the tissues), especially with respect to an acutely toxic dose that is divided into increments and administered in multiple doses over a prolonged period. The latter situation is important because it is applicable to military personnel who, as a result of combat conditions, may be forced to consume field water contaminated by low levels of OP threat agents for as long as seven days. A possible reason to assume that the RBC-ChE is likely to be inhibited to a greater degree than the AChE of tissues under such circumsances is that the red-blood-cell enzyme could serve to protect the AChE of the tissue by acting as a "buffer." Depending on the dose and the rate at which the OP threat agent is absorbed, this "buffer" would interact with some or all of the OP threat agent to limit the amount reaching the tissue.[22,33] Maxwell et al.,[39] Gupta et al.,[40] and Clement[41] all cite published reports that indicate the possibility that other enzymes besides RBC-ChE

might also be involved in such an in vivo detoxification process. These enzymes include aliesterases and butyrylcholinesterase (BuChE) and, although the function of these enzymes is not well known, binding of an OP threat agent to them does not produce toxicity but does reduce the amount of OP threat agent that is available to reach the synaptic junction of neuronal target tissues and the cholinesterase of red blood cells. However, Clement[41] cites evidence from the literature that GA, GB, and GD have a greater affinity for aliesterases than VX, and also showed that BuChE is probably not involved significantly in reducing the amount of GD that can reach the synapses of target tissues. Thus, the affinity of OP threat agents for enzymes that can contribute to detoxification may be an important factor in determining their relative potency, particularly with respect to repeated administration. Nevertheless, RBC-ChE appears to be the last line of defense for preventing G-agents from reaching neuronal tissues and the primary line of defense for preventing VX from reaching such targets. Thus, RBC-ChE should be inhibited to a greater degree than the AChE or other possible sites of target tissues. Additionally, any asymptomatic loss of an enzyme that might contribute to detoxification could make an individual more susceptible to adverse health effects following subsequent exposure to an OP threat agent. Other reasons that the RBC-ChE might appear to be inhibited to a greater extent than AChE of target tissues may be that the AChE activity of the tissues (or even the acetylcholine-receptor sites of the tissues) might recover from inhibition at a rate that would exceed the rate exhibited by the red-blood-cell enzyme,[42] or that detoxifying enzymes recover between doses in cases of repeated administration as indicated by data from experiments performed by Sterri[43] and Sterri et al.,[44] which will be described shortly.

Either alone or together, the mechanisms just mentioned would explain why the onset and severity of symptoms following a particular route of exposure to an OP threat agent appear to be functions of both the total dose and the rate at which this dose is administered and absorbed. For instance, if a dose of OP threat agent were administered and absorbed rapidly, both the RBC-ChE and the AChE of the tissue or any other affected site of synaptic junctions could be inactivated to virtually the same level, and presumably signs and symptoms would develop if the amount of this inhibition exceeded 50%. Alternatively, if a dose of an OP threat agent were administered and absorbed gradually, the AChE enzyme of the red blood cells could have time to intercept and react with the OP threat agent as it is absorbed, limiting most of it from access to the tissues and "buffering" its effect on the activity of the synapses in tissues. Furthermore, if the AChE of the tissue or other affected targets of the synaptic junctions could recover from inhibition faster than the red-blood-cell enzyme, then any initial dose, even a low

one, might depress the activity of both the red-blood-cell and tissue enzyme to nearly the same level, but continued gradual administration and absorption of low doses could allow time for all of the tissue enzyme to recover. Thus, the critical properties and characteristics of synapses, including the amount of AChE needed for tissue function, would always be available, even though the red-blood cell enzyme would continue to be depressed to still lower levels by subsequent doses.

Although the reasons why the RBC-ChE is likely to be inhibited more than the AChE of the tissues are speculative, the available data from laboratory studies support the conclusion that the activity of the red-blood cell enzyme will be more depressed than that of the tissue enzyme, particularly if the process of administration and absorption of the OP threat agent is gradual. For example, Ellin[45] reports that rapidly lowering the cholinesterase activity of the blood in animals to levels near zero by the administration of OP compounds is fatal, but that animals have survived the administration of OP compounds in low concentrations over an extended period, even though the cholinesterase activity of their blood has gradually been lowered to nearly zero in the process. The survival of the laboratory animals following administration of low concentrations of OP compounds over an extended period, even though the cholinesterase activity of their blood approached zero, probably occurred as a consequence of a combination of factors, including the limited inhibition of AChE in tissues. As already mentioned, studies by Sterri[43] and Sterri et al.[44] suggest that one of the factors other than limited AChE inhibition might be the recovery of detoxifying enzymes during the period between doses. In these studies laboratory animals tolerated exposure to a total amount of soman equal to an acutely toxic dose; however, the total amount of soman was divided into several smaller doses that were administered repeatedly over a prolonged period. Another factor, suggested by data from experiments by Gupta et al.[40] is the possibility of adaptation of binding sites following chronic exposure to OP compounds. This adaptation might be in the form of a reduced sensitivity of the noncholinesterase receptors in the ionic channel or a reduction in the number of receptors for binding acetylcholine. Gupta et al.[40] consider adaptation feasible because they observed diminishing severity of effects following administration of an OP compound to rats over time, even before recovery of AChE activity occurred and even when aliesterases were inhibited. More significant are the results of an experiment conducted by Sim et al.,[46] in which 16 military personnel volunteered to drink 2 L/d of water containing a freshly prepared dose of 1.43 μg/kg (100 μg/70-kg individual) of the OP threat agent, VX, each day for a 7-d period (administered daily in four 500-mL doses at 2-h intervals). Although none of them suffered any noticeable signs or symptoms of poisoning, the mean depression of

RBC-ChE for these individuals on the seventh day was about 60% (i.e., RBC-ChE activity was reduced to 40% of normal). Similarly, from their experiments to determine the effects in man of orally and intra-arterially administered sarin (GB), Grob and Harvey[21,22] suggested that the repeated administration to humans of an OP threat agent over several days could gradually reduce the AChE activity of the red blood cells to near-zero levels without the development of any observable signs or symptoms. As discussed previously, the depression of RBC-ChE activity in humans to low levels without the development of observable signs or symptoms after repeated administration of OP threat agents over time is probably due to limited inhibition of AChE in the synapses of target tissues, as well as recovery of detoxifying enzymes between doses and/or adaptation of noncholinesterase binding sites in ionic channels so they become less sensitive to binding OP compounds. However, none of the available experimental data from studies involving laboratory animals or human volunteers indicate that the AChE activity of neuronal target tissues or other properties or characteristics of such tissues essential for function will be affected to a greater degree than that of the RBC-ChE. Thus, RBC-ChE appears to be a conservative benchmark for indicating the possibility of developing acute toxicity following repeated administration of low doses of an OP threat agent over time. The inhibition of RBC-ChE activity is the only indicator of the potential for development of performance-degrading effects consistently cited in the literature.

While gradual administration and absorption of an OP threat agent over a certain period of time may reduce the AChE activity of the red blood cells without producing observable signs and symptoms, gradual administration does not always avoid all effects. The studies of the effect of sarin (GB) on human volunteers from the military[22] showed that individuals who did not exhibit adverse health effects after repeated low doses of the OP threat agent over a single day could develop observable effects from the subsequent administration of equally low doses of the compound on the next day. McNamara et al.[20] attribute this phenomenon to accumulation of effective dose and imply that the amount of accumulation will depend on both the rate of dosing and the rate of recovery of the functional AChE activity of the tissues. However, more recent studies by D'Mello and Duffy,[47] and by Gupta et al.[48] note that the recovery of functional AChE and RBC-ChE occur at a slower rate than recovery from observable symptoms. Therefore, it is the recovery rate of the functional activity of affected synaptic junctions that is most meaningful with regard to estimating MPCs for OP threat agents with the use of a model. Nevertheless, McNamara et al.[20] do point out that one important measure of effective dose is indicated by depression of AChE because an OP threat agent itself does not seem

to accumulate in humans. Furthermore, once combined with AChE, there is no known function for the complex, and should the enzyme become reactivated, the aged residual is inert.

Thus, there are four factors we consider relevant for developing interim field-water-quality standards for the OP threat agents of concern. The first one is the dose of the compound and its daily rate of administration. The second factor is the rate of recovery from sublethal effects, which is related to restoration of nervous-system function and not to reactivation of the AChE activity of the red blood cells that is inhibited coincidentally.[21,22,25,33,42] The third factor is the correspondence between the development of signs and symptoms and any single or accumulated effective dose as measured by depression of the activity of the AChE enzyme,[20] where the inhibition of RBC-ChE is assumed to reflect the degree to which the tissue AChE has been inhibited. The last factor is the threshold (i.e., fraction) of AChE inhibition (as indicated by RBC-ChE depression) above which performance-degrading effects might occur in exposed military personnel. The value of the threshold for performance-degrading effects is discussed next in more detail. The values for the other three factors are described in the section explaining the calculation of maximum permissible concentrations (MPCs) for consideration as field-water-quality standards.

As we stated earlier, Sim and Stubbs[38] proposed a correlation between the depression of RBC-ChE and the onset of acute symptoms based on the analysis of the responses of subjects who received a single percutaneous dose of the OP threat agent, VX. According to their assessment, no performance-degrading health effects are likely until the AChE of red-blood cells has been depressed below 50% of normal activity. Notwithstanding, Grob and Harvey[21] suggest that a single oral exposure to an OP threat agent sufficient to depress the AChE of red blood cells to a level of 25% of normal (75% reduction in activity) is necessary before health effects will be observed. In addition, Gage[49] states that evidence from his survey of the literature suggests that for those OP anticholinesterase compounds that inactivate RBC-ChE before the pseudocholinesterase of plasma, toxic effects probably will not occur unless the RBC-ChE activity is depressed below 25% of normal (75% reduction in activity). However, for occupational exposure to OP anticholinesterase compounds, Gage[49] recommends the removal of workers from their place of employment when either the AChE of the red blood cells or the pseudocholinesterase of the plasma falls to 70% of its normal value (30% depression), so that further absorption will not lead to deterioration of health (not due to any immediate risk of toxic effects). Gage[49] indicates that when the measured blood-enzyme level returns to 80% of normal (20% depression), the employee can return to work. The

occupational safety and health standards of the U.S. Department of the Army for (1) removing employees from work involving the production, packaging, repackaging, storage, demilitarization, transportation, handling, use, and/or disposal of the OP threat agent, GB, and for (2) permitting their return to such work is in general agreement with Gage's recommendations.[50] Accordingly, the U.S. Department of the Army[50] criteria for (1) removing the previously described employees from their work environment is reduction of an individual's baseline value for the RBC-ChE activity to a level below 75% (a depression of more than 25% of normal activity) and for (2) permitting an employee to return to work is restoration of the individual's RBC-ChE activity to a level of at least 80% of the baseline value and the absence of symptoms for at least 1 wk.

Based on the available data, it is reasonable to assume that anytime the AChE activity of red blood cells is depressed below 50% of normal in exposed military personnel, the general performance of these individuals could be impaired. Consequently, 50% depression of RBC-ChE is considered an appropriate threshold upon which conservative estimates of maximum permissible concentrations (MPCs) can be based. Accordingly, such MPCs may be recommended as interim field-water-quality standards for the OP threat agents for military personnel consuming up to 5 or 15 L/d of contaminated field water over a 7-d period. However, there are uncertainties concerning whether or not individuals will be forced to reenter environments contaminated by OP threat agents shortly after having been in such environments and exposed to contaminated field water for 7 d. For example, the AChE activity of the red blood cells of these individuals may be depressed up to 50% of normal after an initial 7-d exposure period and, as Grob and Harvey[22] showed in their experiments with sarin (GB), these individuals may be susceptible to toxic effects from any subsequent dose(s) that previously did not produce symptoms. It is also possible that subtle and less obvious neurobehavioral changes, which may have serious consequences for pilots and other military personnel operating complicated machinery and weapons systems, may be associated with reduction of the AChE activity to levels less than 50% of normal, as measured by RBC-ChE depression. We also calculate MPCs for consideration as standards based on a reduction of the activity of RBC-ChE to a level of 80% of normal (20% depression) for use if military planners and medical experts believe that additional conservatism needs to be incorporated in the recommended field-water-quality standards for the OP threat agents in order to protect military personnel from such health consequences.

We suggest that the inhibition of only 20% of RBC-ChE activity is a very conservative figure for military personnel under combat conditions because there are no data associating this level of depression with any human health effects, subtle or obvious.

However, the 20% figure for inhibition does represent the action level for permitting U.S. Department of the Army employees to return to a work environment involving actual or potential contact with the OP threat agent. GB.[50]

CALCULATION OF MPCs

The relationship between a continuous dose of a compound to a particular target tissue or organ (i.e., a biological compartment) and the body burden or accumulation of the compound after a specified time can be described mathematically as

$$X = \frac{Y}{r} [1 - \exp(-rt)] , \quad (1)$$

where

X = accumulated effective dose of a compound (μg of compound/kg of body weight);
Y = daily rate of intake of a compound [μg/(kg•d)];
r = rate of removal of a compound from its target tissue or rate of recovery from the effects of the compound (1/d); and
t = time after exposure (d).

An important element in Eq. 1 is the rate of removal of the compound from the affected target tissue, or, equivalently, the rate of recovery from the effects of the compound. The appearance of the compound at the target tissue or organ may be considered instantaneous after exposure; the rate of removal of the compound from the target tissue (r) is based on its effective biological half-life. Consequently, Eq. 1 is the expression for an exponential compartmental model and, as done by McNamara et al.[20] and McNamara and Leitnaker,[51] has been adapted to address the biological behavior of the OP threat agents. This approach was adopted for estimating MPCs for the OP threat agents of concern because it is compatible with the limited data available concerning the mechanisms of toxicity for these compounds. In fact, even though the time course and severity of toxicity might differ depending on whether an OP threat agent predominantly affects target tissue of the central or peripheral nervous system, few data are available concerning such differences. Consequently, the assumption that is made that an OP threat agent can appear at target tissue instantaneously following exposure by ingestion is probably a conservative one.

By introducing a conversion factor [k, (%•kg)/μg] into Eq. 1 to account for the correspondence between an administered dose of an OP threat agent and the potency of the compound in depressing the activity of RBC-ChE (i.e., $kX = k[Y/r][1 - \exp(-rt)] = Q$,

% RBC-ChE depression), we obtain an equation that is suitable for predicting either (1) the daily dose of an OP threat agent [Y, μg/(kg•d)] or (2) the accumulated effective dose (X, μg/kg) after time t (d) based on the percentage decrease in RBC-ChE activity. Consequently, the daily dose [Y, μg/(kg•d)] can easily be converted to a field-water concentration (C, μg/L) by multiplying it by the factor W/D, which is the assumed standard weight of military personnel (W = 70 kg) divided by their maximum daily field-water consumption rate (D = either 5 or 15 L/d). Thus, by (1) introducing the factors k and W/D on both sides of Eq. 1, (2) substituting Q for kX on the left side of the equation, and C for Y(W/D) on the right side, and then (3) solving the resulting equation for C, we derive the equation for calculating MPCs for consideration as field-water-quality standards:

$$C = \frac{Q\, r\, W}{k\,[1 - \exp(-rt)]\, D}\ , \qquad (2)$$

where

C = maximum permissible concentration (MPC) of an OP threat agent in field water for consideration as a recommended interim field-water-quality standard (μg/L);

Q = amount of inhibition of tissue AChE activity, as indicated by depression of RBC-ChE activity, representing threshold above which health effects could occur (%);

r = recovery rate of the nervous system (and presumably the activity of the tissue AChE) from acute toxicity (1/d);

k = conversion factor describing the potency of a dose of an OP threat agent in terms of the percentage decrease in RBC-ChE activity per μg of OP threat agent administered per kg of body weight [(%•kg)/μg];

t = time over which repetitive dosing occurs (d);

W = standard weight assumed to be applicable to the population of exposed military personnel (kg); and

D = daily drinking-water consumption rate (L/d).

To solve Eq. 2, the value of Q is either 50 or 20%; the values of r and k are specific for each OP threat agent; the value of t corresponds to a maximum exposure period for military personnel of up to 7 d; the value of W is 70 kg; and the value of D is either 5 or 15 L/d.

In Eq. 2 the values selected for W, D, and t (70 kg, 5 or 15 L/d, and 7 d, respectively) are presumed to be appropriate for populations of military personnel consuming field water in environments contaminated by OP threat agents. The value selected for Q (either 50 or 20% inhibition of RBC-ChE) in Eq. 2 is considered to be a conservative or

very conservative approximation of the threshold for inhibition of RBC-ChE, above which performance-degrading health effects could develop in exposed military personnel. Because the values for k and r in Eq. 2 are compound-specific, we had to survey the literature for data that would allow us to estimate the value of these parameters for each of the OP threat agents of concern. The values for these parameters are presented next, along with a discussion of their derivation.

To obtain values for k, the factor relating the potency of a dose to the amount of RBC-ChE depression, we had to examine the potency of these compounds relative to oral administration in humans. It is important to consider ingestion as the route of exposure because data reviewed by Dacre,[8] and reported by Sidell and Groff,[9] and Schoene et al.[52] all provide evidence that the toxicity of these compounds differs, depending on the route of administration. Equally important is assessment of the relative toxicity of these substances from human data, if possible, because according to Ellin[45] the effects of OP poisoning may or may not be parallel in different animal species. This is illustrated by data reported by Boskovic et al.,[53] indicating that GD toxicity is 12.6 times greater in dogs than in mice, 3.3 times greater in guinea pigs than in mice, and 1.5 times greater in rats than in mice, and that the toxicity of tabun is about the same in mice, rats, and dogs, but 2.4 times lower in guinea pigs.

Sidell and Groff[9] compared the dose of VX that inhibited RBC-ChE activity by 50% in military personnel who volunteered to receive a single dose of VX administered orally in water with the single dose of sarin (GB) reported by Grob and Harvey[22] to produce the same effect after similar administration to another group of military volunteers. According to this comparison, the single oral doses of VX and GB needed to achieve 50% depression of RBC-ChE in humans are 2.3 and 10 μg/kg of body weight, respectively. Therefore, VX is considered to be approximately four times more potent than GB by this route of exposure, and we estimate the value of k for VX and GB to be about 20 and 5 (%•kg)/μg (i.e., 50/2.3 and 50/10), respectively. The assumption is also made that for repetitive equal oral doses of an OP threat agent administered over several days, the value of k determined after any successive dose will be constant. However, this assumption is very conservative because experiments by Grob and Harvey[22] involving the administration of repeated doses of sarin (GB) to volunteer military personnel revealed that the amount of RBC-ChE inactivated after each successive dose decreased progressively. Furthermore, Sim et al.[46] showed a similar progressive decrease in the average daily depression of RBC-ChE activity for 16 military personnel who volunteered to drink a freshly prepared dose of 100 μg/70 kg of body weight (1.43 μg/kg of body weight) of VX in 2 L of water administered in four 500-mL doses at 2-h intervals each day for 7 d. Thus, it

appears that there is some nonlinear relationship between k and time post administration; however, due to the limited nature of the available data, the most conservative values for k were employed, which are those based on single oral doses.

Unfortunately, quantitative data describing the relationship between an oral dose for humans and the corresponding amount of RBC-ChE depression are not available for either soman (GD) or tabun (GA). Therefore, to determine the k value for GD and GA, we need to establish the potency of these compounds relative to VX and/or GB with respect to RBC-ChE depression.

Grob and Harvey[22] state that GB is about five times more potent in inhibiting human RBC-ChE than is GA. Based on extrapolation of all animal experiments involving GA and GD to man, Boskovic et al.[53] conclude that GD is about 10 times more toxic than GA in humans. The study by Boskovic et al.[53] was the only one that attempted to estimate the relative toxicity between GD and another OP threat agent of concern with respect to humans. However, oral-rat LD50 data (median lethal dose to an exposed population of laboratory animals) reviewed by Dacre[8] generally support the conclusion of Boskovic et al.[53] concerning the relative potencies of GD and GA. Other data from studies involving laboratory animals reviewed by Dacre[8] also show that for oral administration VX can be considered the most potent of the OP threat agents of concern, followed by GD, GB, and then GA. Such relative toxicity between these compounds may be correlated with differences in their ability to preferentially inactivate RBC-ChE (and presumably all AChE). For example, Sidell and Groff[9] report that most OP anticholinesterase insecticides (e.g., parathion) inhibit BuChE more than RBC-ChE. GB, once considered the most potent OP threat agent,[22] inhibits RBC-ChE slightly more than do the insecticides, and VX inhibits RBC-ChE almost exclusively. Additionally, Boskovic et al.[53] indicate that GD tends to preferentially bind to RBC-ChE.

Based on the information about k values and the relative potencies of the OP threat agents just described, the k values for ingested VX, GD, GB, and GA can now be derived relative to one another. The value of k for GB is estimated to be 5 (%•kg)/μg, or one-fourth of the value of k for VX (20 [%•kg]/μg); the value of k for GA is estimated to be one-fifth of the value of k for GB (or 1/20 the value of k for VX); and the value of k for GD is estimated to be about 10 times the value of k for GA (or one-half the value of k for VX). In summary, VX appears to be twice as potent as GD, four times as potent as GB, and 20 times as potent as GA following ingestion. The numerical estimates for k for each of the OP threat agents of concern are presented in Table 1.

The value of r, which is the recovery rate from toxicity, for each of the OP threat agents was also determined from a literature survey. It is important to reemphasize that

Table 1. Summary of estimated values for potency (k) and recovery (r) for each of the OP threat agents of concern.

OP threat agent	k [(%•kg)/μg]	r (1/d)
VX	20	0.40
GD (soman)	10	0.05
GB (sarin)	5	0.10
GA (tabun)	1	0.10

the value of r is a measure of the functional recovery of neuromuscular activity and that this recovery parallels clinical recovery of the tissue and is not related to the rate of recovery of RBC-ChE, which is much slower. In fact, Sidell[42] reports that in an accidental case of poisoning by soman (GD), a compound that rapidly ages cholinesterase and thereby makes it resistant to spontaneous or therapeutic reactivation, the patient's course of recovery suggested that either the tissue cholinesterase recovered more rapidly than the cholinesterase in the circulatory system, or that the patient could function with a negligible amount of tissue cholinesterase present. The values of r that we chose to use for each of the OP threat agents of concern are described next and also appear in Table 1.

According to McNamara and Leitnaker,[51] evidence from experiments with guinea pigs exposed to GB shows that recovery of both BuChE (plasma cholinesterase) and specific brain cholinesterases correlate with the animal's recovery from toxicity. Based on these data and the absence of any other data to indicate that human cholinesterases might respond differently, these researchers assume that the guinea-pig model can be generalized to man. Therefore, the recovery of BuChE is considered to be a suitable measure of recovery from clinical symptoms for humans. Based on this reasoning and the work of Grob and Harvey,[22] who orally administered GB in water to human volunteers and then measured both RBC-ChE and BuChE depression and recovery, McNamara and Leitnaker[51] calculated that the recovery of GB-depressed BuChE and, therefore, recovery from toxicity, is 10% per day (i.e., r = 0.1/d). In another report, McNamara et al.[20] computed the recovery constant for that small amount of BuChE that can be depressed by VX to be 40% per day (i.e., r = 0.4/d). This calculation was based on data obtained from experiments with military volunteers. Because of the pharmacological similarities between VX and GB, and the fact that the BuChE activity following depression by both GB and VX was shown to have an exponential recovery rate, these researchers once again

assumed that for humans the recovery of VX-depressed BuChE activity parallels recovery from toxicity. McNamara et al.[20] attribute the more rapid recovery from VX poisoning to the ability of inactivated AChE to undergo spontaneous reactivation, a phenomenon not associated with inactivation of AChE by GA, GB, or GD.

It is assumed that the recovery rate of GA is equivalent to that of GB, based on the pharmacological similarities between GB and GA discussed by Grob and Harvey,[22] particularly the fact that both GB and GA combine with cholinesterase almost irreversibly during the first hour of their reaction. Finally, based on data reported by Dettbarn[54] concerning the half-life of AChE inhibition following GD exposure in different rat tissues, including the brain (14.5 d), and assuming that (1) this recovery rate for rat-brain AChE can be generalized to humans and that (2) in humans the rate of recovery of brain cholinesterase is exponential and parallels recovery from toxicity, as was considered applicable for GB and VX,[20,51] we estimate the value of r for GD to be 5% per day [i.e., (ln 2)/14.5 d]. Interestingly, the half-life of AChE inhibition in the brain that was observed by Dettbarn[54] was the longest recovery rate for AChE of all the tissues examined, including peripheral nerve tissue; hence, we consider our estimate of r for GD to be conservative.

Table 2 contains MPCs for each OP threat agent of concern that were calculated for consideration as standards on the basis of the depression of RBC-ChE activity not exceeding more than 50% of normal in 70-kg military personnel consuming up to 5 or 15 L/d of field water over a 7-d period. For comparison and further consideration by military planners, Table 3 presents MPCs calculated on the basis of the depression of RBC-ChE activity not exceeding more than 20% of normal in 70-kg military personnel consuming up to 5 or 15 L/d of field water over a 7-d period. Each of the values presented in Tables 2 and 3 was determined using Eq. 2 and the applicable k and r values from Table 1.

The exponential single-compartment model for estimating MPCs for the OP threat agents of concern was applied because, at this time, data do not support determination of MPCs by other, more complicated modelling strategies. Also, a model was needed to estimate MPCs for GA and GD because experiments in which human volunteers repeatedly ingested drinking water contaminated with low concentrations of OP threat agent over the course of several days and from which MPCs could be derived are limited to two studies involving VX and GB. Additionally, the continuous exposure feature of the model is considered to reflect slow absorption of low doses of OP threat agents from the gastrointestinal tract, as indicated to occur following oral administration of VX.[9] Such slow absorption from the gastrointestinal tract suggests that ingestion of several low doses

Table 2. Maximum permissible concentrations (MPCs) for the OP threat agents of concern, based on RBC-ChE activity not being depressed by more than 50% of normal in 70-kg military personnel with field-water consumption rates of 5 and 15 L/d for up to 7 d.

OP threat agent	Consumption rate and corresponding MPC (μg/L)	
	5 L/d	15 L/d
VX	15	5.0
GD (soman)	12	4.0
GB (sarin)	28	9.3
GA (tabun)	140	46

Table 3. Maximum permissible concentrations (MPCs) for the OP threat agents of concern, based on RBC-ChE activity not being depressed by more than 20% of normal in 70-kg military personnel with field-water consumption rates of 5 and 15 L/d for up to 7 d.

OP threat agent	Consumption rate and corresponding MPC (μg/L)	
	5 L/d	15 L/d
VX	6.0	2.0
GD (soman)	4.7	1.6
GB (sarin)	11	3.7
GA (tabun)	56	18

of an OP threat agent separated in time over the course of a day might effectively act as one dose administered continuously throughout the day. However, before any of the MPCs obtained from applying the model can be recommended for consideration as interim field-water-quality standards for OP threat agents, a comparison needs to be made between calculated MPCs or corresponding daily doses and comparable MPCs or corresponding daily doses derived from available empirical data obtained in studies involving repeated ingestion of OP threat agents by human volunteers over several days. There are several reasons why such supporting data are necessary. First, a threshold for inhibition of RBC-ChE activity used in the model is an effect that is suitable only as an indicator of the potential for an individual to develop adverse health effects that could be performance degrading. Unfortunately, on the basis of the data available in the literature, no other, more direct measurement for relating the dose of an OP threat agent

to a performance-degrading response is suitable and can be used. Second, the amount of RBC-ChE activity lowered by a dose of an OP threat agent (k) might vary widely between individuals, as indicated by the study with VX performed by Sidell and Groff[9] using human volunteers. Third, recovery from inhibition of another enzyme, BuChE, was used as an indicator of recovery (r) of tissue function. Yet, the rate of recovery of the BuChE enzyme or the function of neuronal tissue itself may also vary markedly between individuals and among species. Unfortunately, details about the recovery process of neuronal tissue are not well described in the literature and no better indicator for recovery of neuronal function has been recommended, even though other enzymes systems are probably involved in the recovery process. Furthermore, BuChE recovery was estimated in the literature from human data for VX only, a recovery rate for BuChE was based on animal data for the other OP threat agents.

As a means of testing the suitability of the model, calculated MPCs or corresponding daily doses were compared with those that can be derived from available empirical data obtained in studies involving repeated ingestion of OP threat agents by human volunteers over several days. The closer the approximation, the more confidence can be placed in the model, especially with regard to estimating MPCs for GA and GD. These comparisons are presented next.

COMPARISON OF DAILY DOSES BASED ON MPCs WITH THOSE ADMINISTERED IN STUDIES WITH HUMAN VOLUNTEERS

As mentioned previously, there are two studies of particular interest involving oral administration of OP threat agents to human volunteers. First is the study reported by Grob and Harvey,[22] in which GB was administered orally to military volunteers at the rate of 8 to 16 μg/kg of body weight at an average interval of 7.4 h over 3.5 d. Second is the study reported by Sim et al.,[46] in which VX was administered orally in water to 16 military volunteers for a period of 7 d at a dose rate of 1.43 μg/kg of body weight (100 μg/70 kg of body weight) per day. For GB, a total dose of 88 μg/kg over 3 d (equivalent to 29.3 μg/kg per day for 3 d) or 6 mg per 70-kg individual, was needed to induce mild symptoms in exposed volunteers. For VX and a dose rate of 1.43 μg/kg per day for 7 d, the total dose of 0.7 mg per 70-kg individual did not induce any signs or symptoms of poisoning in the 16 exposed volunteers, even though the average RBC-ChE activity for these individuals was depressed to 40% of normal (60% inhibition) on the seventh day.

Converting the concentration values in Table 2 for VX and GB into daily dose rates of OP threat agent per kg of body weight yields values of approximately 1.1 μg/kg per day for VX and 2.0 μg/kg per day for GB. The converted daily dose rate for VX is smaller than the one that produced no signs or symptoms in human volunteers after 7 d [i.e., 1.43 μg/(kg•d)]. Similarly, the converted daily dose rate for GB is smaller than the one that produced mild symptoms in human volunteers after 3 d [i.e., 29.3 μg/(kg•d)]. Furthermore, according to Grob and Harvey,[22] a single dose of GB of 16 μg/kg administered orally should not produce any symptoms in exposed individuals, and even small divided doses of GB totalling 30 μg/kg after one day should not produce symptoms until subsequent doses are administered on the second or third days of administration. Therefore, we do not expect a daily dose rate of GB of 2.0 μg/kg of body weight over 7 d to produce symptoms because, even after 7 d, the total dose will not exceed 16 μg/kg. More support for this conclusion comes from the fact that Grob and Harvey[22] indicate that after a single dose of GB, symptoms were usually coincident with depression of RBC-ChE activity to 22% of its original level (78% inhibition), and our calculated MPCs presented in Table 2 for both VX and GB are based on the depression of RBC-ChE activity not exceeding 50% of normal for an exposure period lasting up to 7 d.

Unfortunately, dose-effect data with respect to repetitive oral administration of GD and GA to human volunteers are not available for comparison, and therefore we must rely on inferences from available data to justify our results. For example, from the publication of Grob and Harvey,[22] we infer that although the potency of GB is greater than the potency of GA by a factor of 5, the rate of recovery from symptoms will be the same for both compounds after repeated administration of subacute doses each day for up to 7 d. Therefore, for both compounds, the cumulative dose associated with a particular effect should only differ by a factor of about 5; this is reflected in our estimates of MPCs for field water for these compounds (see Tables 2 and 3). Similarly, we estimated the potency of VX to be twice that of GD, based on a single oral dose, but we consider the recovery from symptoms induced by subacute doses to be eight times greater for VX than for GD because AChE inhibited by VX can undergo spontaneous reactivation,[20] and GD rapidly ages cholinesterase, making it resistant to therapeutic and spontaneous reactivation.[4,55,56] Thus, the dose of VX that can cause a particular cumulative effect on RBC-ChE activity and produce symptoms when administered orally over several days should differ from the dose of GD that produces the same consequences when administered in the same manner by a factor of much less than 2. Our estimates of almost equal values for MPCs in field water for these two compounds is consistent with this conclusion (see Tables 2 and 3).

RECOMMENDED INTERIM FIELD-WATER-QUALITY STANDARDS FOR OP THREAT AGENTS

A comparison of the calculated MPCs in Tables 2 and 3 for the OP threat agents of concern for 5- and 15-L/d consumption rates reveals that the concentrations computed for GD for both 20 and 50% inhibition of RBC-ChE are the lowest ones. The reason that the calculated MPCs for GD are so low is related to the fact that GD not only is a relatively potent inhibitor of cholinesterase but also is the quickest and most effective of the OP threat agents in aging cholinesterase (i.e making it refractory to reactivation).[4,55,56] None of the other OP threat agents possesses both of these properties. For example, even though VX is a more potent inhibitor of cholinesterase than GD, it dotes not age cholinesterase as quickly or effectively as GD. Therefore VX is not as cumulative a poison and life-saving therapeutic reactivation of cholinesterase may be possible. In fact, even though some detoxifying mechanisms might exist, GD is considered to pose the greatest threat to military personnel,[26] presumably because of its ability to rapidly age cholinesterase and make it resistant to reactivation, particularly reactivation by therapeutic drugs. Based on this reasoning and in consideration of 50% inhibition of RBC-ChE as a conservative estimate of the threshold above which performance-degrading effects could occur in military personnel exposed to OP threat agents in field water, we recommend that the MPCs for GD shown in Table 2 (i.e., 12 μg/L and 4 μg/L for consumption rates of 5 and 15 L/d, respectively) be considered for adoption as the interim field-water-quality standards for all of the OP threat agents of concern. Another important reason for recommending that the field-water-quality standards for all the OP threat agents of concern be based on the lowest ones we derived (i.e ., those for GD) is that the current test procedure for determining the presence of toxic concentrations of OP threat agents in field water is a nonspecific one--that is, it is based on the inhibition of eel cholinesterase enzyme by any OP anticholinesterase compound.

Our recommendation for interim field-water-quality standards for the OP threat agents of concern are lower than the current short-term field-water-quality standard for nerve agents now used by the U.S. Army (i.e, 20 μg/L).[57,58] However, our recommendation is based on consideration of the cumulative effect of these compounds, as well as their immediate potency, both of which are important factors and need to be addressed with regard to field-water-quality standards for this class of compounds. Moreover, our recommendation to base the standard for OP threat agents on depression of RBC-ChE to 50% of normal by GD does not take into consideration the possibility that there will be enough time prior to exposure to OP threat agents for field commanders to

consider enforcing medical doctrine for pretreatment. The doctrine recommends that military personnel with the potential for exposure to OP threat agents undergo pretreatment with pyridostigmine bromide (i.e., a carbamate compound that binds reversibly to acetylcholinesterase and is administered for prophylaxis) beginning just prior to and continuing throughout the exposure period (i.e., 30-mg tablets taken orally 3 times per day). This doctrine is contained in Section 5 of Field Manual 8-285: Treatment of Chemical Agent Casualties and Conventional Military Chemical Injuries,[59] which was just published. Also explained in Field Manual 8-285 is that for pyridostigmine bromide to be an effective pretreatment (i.e., by preserving enough of the AChE enzyme in a reversibly bound form to allow pretreated individuals to survive exposure to OP threat agents, especially to those agents which irreversibly bind to AChE), a pretreated individual must also administer nerve-agent antidote (i.e., 2-PAM and atropine) upon actual exposure.

The impact of pretreatment with pyridostigmine bromide would be lower than normal RBC-ChE levels in pretreated individuals prior to any exposure to OP threat agents. Accordingly, under this scenario there is the possibility that pretreated individuals consuming field water with an OP threat agent at a concentration associated with 50% depression of RBC-ChE (see Table 2) might experience adverse health effects that can be considered incapacitating. Consequently, if pretreatment with pyridostigmine bromide is employed and such pretreatment depresses RBC-ChE activity by a level less than or equal to 30% (i.e., to 70% of normal), then we recommend that interim field-water-quality standards for OP threat agents be based on those calculated MPCs for GD that are shown in Table 3. These MPCs for field water are based on RBC-ChE activity not being depressed by more than 20% (i.e., to 80% of normal).

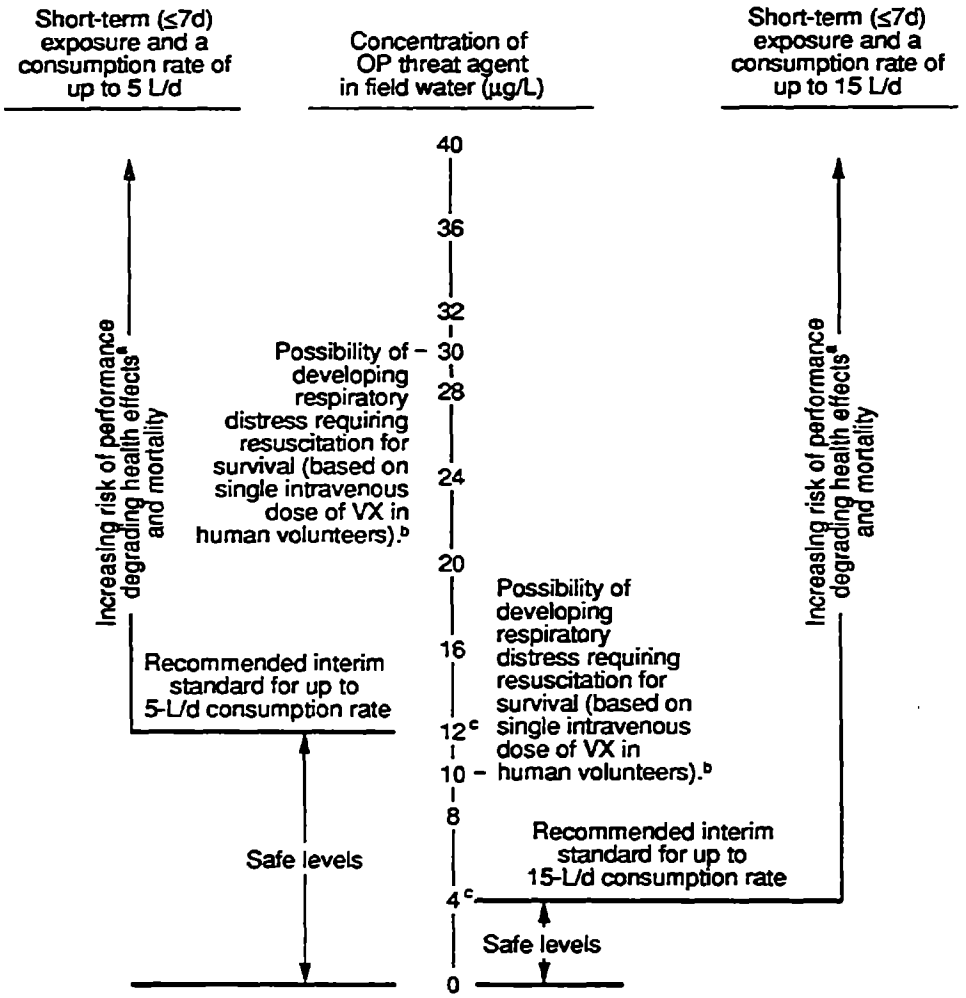
Finally, if 20% inhibition of RBC-ChE is deemed more appropriate for a field-water-quality standard--for example, because of performance criteria for military personnel operating complicated equipment (e.g., aircraft, weapons systems, heavy machinery), we propose that the calculated MPCs for GD shown in Table 3 be used as interim field-water-quality standards for the entire class of OP threat agents. However, such values are very conservative because it is only speculative at this time that 20% RBE-ChE depression could represent the threshold above which impaired performance could occur and be significant from any military perspective. However, as mentioned before, basing the OP threat agent standards for field water on 20% depression of RBC-ChE by GD does have the potential advantage of protecting military personnel pretreated with pyridostigmine bromide from possible incapacitation (if RBC-ChE levels are depressed by carbamate pretreatment to levels less than or equal to 70% of normal).

RISK ASSESSMENT

Figure 2 is a visual guide for assessing the impact of OP threat agent concentrations in field drinking water supplies that exceed the recommended interim standards for 5 and 15 L/d consumption rates. The figure shows that concentrations of OP threat agents in field water greater than the MPCs recommended as interim standards can produce performance-degrading health effects that can include abdominal cramps, vomiting, diarrhea, and headache. Sufficiently high levels consumed over the course of a 7-d period may even lead to mortality. However, the concentration of OP threat agents at which lethality might occur from repeated ingestion in drinking water over the course of several days is not reported in the literature. Consequently, an estimate of that level is noted in the figure from data for VX, but this estimate is probably conservative because it is based on a single intravenous dose in humans. Because OP threat agents are designed to be poisonous, there is probably a narrow margin between safe levels in water and those producing performance-degrading health effects, even under circumstances where an OP threat agent is ingested in several drinks separated in time over the course of a day for an exposure period lasting up to 7 d.

SUMMARY AND CONCLUSIONS

The recommended interim field-water-quality standards for OP threat agents for consumption rates of 5 and 15 L/d are 12 and 4 μg/L, respectively. These standards are less than the standard for OP threat agents currently used by the military (i.e., 20 μg/L) and were derived using inhibition of RBC-ChE activity below 50% of normal as an indicator of the potential for performance-degrading health effects to develop. A simple model was employed that accounted for both the potency of OP threat agents to produce performance-degrading health effects and the recovery from such effects. This model was necessary because a dose of OP threat agent divided into smaller doses that are separated by time over the course of a day is less toxic than the same dose ingested all at one time. This difference in toxicity is probably due to the presence of detoxifying



[a]Performance-degrading health effects can include abdominal cramps, vomiting, diarrhea, and headache.

[b]Response considered possible on the basis of a single intravenous dose of VX in humans of 2.12 µg/kg converted to a drinking water concentration. This response and corresponding concentration are presented because lethality data for repeated ingestion of OP threat agents over time are not available for humans. Furthermore, VX is the most toxic OP threat agent when administered intravenously in a single dose to humans, but appears to be less toxic than GD when ingested in several divided doses over time.

[c]Interim standards for OP threat agents are based on the MPC for GD because GD appears to be the most toxic OP threat agent where a total dose from field water is ingested in several drinks separated in time over the course of a day for an exposure period lasting up to 7 d.

Figure 2. Health-effects summary for OP threat agents in field water (recommended interim standards appearing in the figure equate to depression of RBC-ChE by GD to 50% of normal; recommended interim standards that equate to depression of RBC-ChE by GD to a level that is 80% of normal are 4.7 and 1.6 µg/L for consumption rates of 5 and 15 L/d, respectively, and are for consideration if pretreatment with pyridostigmine bromide is a possibility).

enzymes and other mechanisms that are not overwhelmed by a single dose and can undergo recovery in the period between ingestion of smaller doses over the course of a day. The limited data available from studies involving human volunteers ingesting OP threat agents for several days compared favorably with results for similar compounds using the model. Because the data from which the MPCs were calculated are limited, the recommended standards are considered interim.

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CHAPTER 5. THE TRICHOTHECENE MYCOTOXIN T-2

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INTRODUCTION

Mycotoxins are metabolites of fungi that are produced by secondary biochemical pathways. These pathways are active when changes in chemical and physical conditions restrict fungal growth. Mycotoxins have been implicated as the causative agents of adverse health effects in humans and animals that have consumed fungus-infected agricultural products and plants.[1-2] Consequently, the fungi that produce mycotoxins, as well as the mycotoxins themselves, are potential problems from both a public-health and an economic perspective. Additionally, one chemically related group of mycotoxins, the trichothecenes, may also represent a problem from a military perspective because of their potential use as a threat agent.

In 1981, the trichothecene mycotoxin T-2 was claimed to be the lethal ingredient in the yellow spots that appeared on some rocks and leaves and in water samples taken from locations near battlefields in Laos and Kampuchea.[3-4] This trichothecene mycotoxin purportedly was aerially dispersed as a chemical weapon--yellow rain--described by inhabitants from these combat zones in Southeast Asia, and from places in Afghanistan where military engagements had also taken place, as aerial attacks where yellow granules or mists were released that "fell like rain" and produced disease.[5] Further implicating the use of mycotoxins as chemical weapons is evidence reported by Watson et al.[6] that environmental samples consisting of leaves and scrapings from rocks obtained from victims of chemical attacks in Southeast Asia contained concentrations and combinations of mycotoxins not frequently found naturally on such surfaces. Yet, the evidence for the use of chemical weapons comprised of trichothecene mycotoxins, particularly T-2, remains controversial. For example, even though T-2 toxin or its metabolite HT-2 are reported to have been present in the blood, urine, or tissues of 20 individuals alleged to have experienced such chemical attacks,[4] the source may actually have been contaminated food.[3] Moreover, according to Seeley et al.,[4] the statements about yellow rain by alleged victims are ambiguous and conflicting; the results from the analyses of the environmental samples collected in the field and then analyzed by different research laboratories and at different times are contradictory; and most important of all, the physical composition of the yellow spots themselves indicates they could be

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of natural origin—excrement released by Asian honeybees in fecal showers as they swarm unheard and unseen overhead.

Despite this controversy, T-2 toxin is one of the most toxic trichothecenes, particularly if ingested. The biosynthesis of trichothecene mycotoxins from Fusarium fungi has been performed in the laboratory, where chemical and physical conditions can be changed to influence the quantity and composition of the secondary metabolites that are produced.[5] For example, Cullen et al.[7] describe a procedure for producing high levels of T-2 toxin from Fusarium (i.e., milligram quantities per litre of medium) and mention possible improvements that can be made to the process so that even greater yields (i.e., gram quantities per litre of medium) could be obtained inexpensively to satisfy research needs. Conceivably, such processes might be adapted to produce sufficient quantities of the most toxic trichothecene mycotoxins, particularly T-2, for incorporation into chemical weapons. In fact, according to Watson et al.,[6] the decision to test samples of "yellow rain" from locations in Southeast Asia where such attacks were reported was based in part on a review of existing information concerning trichothecene mycotoxins. That review revealed (1) trichothecene mycotoxins possess chemical, physical, and toxicological properties that make them candidates for use as chemical weapons; (2) the technology to manufacture significant quantities of the compounds is available; and (3) studies have been performed with trichothecene mycotoxins at research facilities linked to research on chemical and biological weapons. Thus, mycotoxins, especially T-2, represent potential threat agents and are of military concern in field water. In this chapter we develop recommendations for interim field-water-quality standards for the trichothecene mycotoxin T-2 that will protect military personnel consuming up to 5 or 15 L/d of water during an exposure period lasting up to 7 d.

As discussed by the National Research Council (NRC) Committee on Protection Against Mycotoxins,[5] definitive data describing the relationship between human health effects and exposure to a specific mycotoxin have only been reported for the trichothecene mycotoxin, diacetoxyscirpenol (DAS, or anguidine). The reason such data even exist for DAS is that DAS has been administered in clinical trials designed to evaluate its chemotherapeutic efficacy in treating cancers. However, data derived from laboratory experiments with animals and summarized by the NRC Committee on Protection Against Mycotoxins[5] indicate T-2 toxin and DAS have similar toxicological properties and modes of action, even though they differ slightly in chemical structure. Therefore, we describe the relevant chemical and toxicological similarities between T-2 toxin and DAS and then use the available dose-response data for human toxicity reported for DAS to derive recommendations for field-water-quality standards for T-2 toxin.

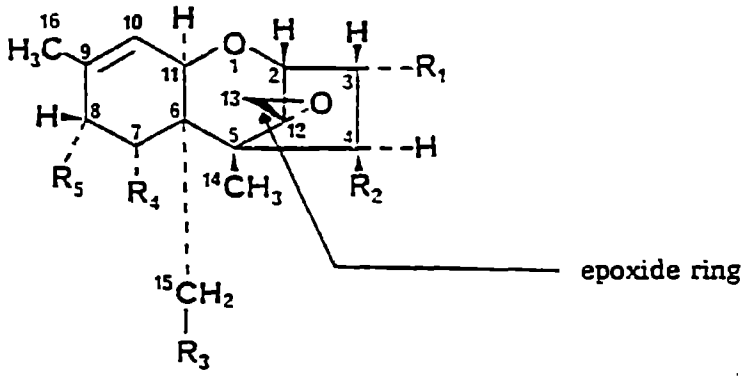
Dose-response data for the toxicity of T-2 toxin in animals are also evaluated with respect to extrapolation to humans to support our recommendations.

OCCURRENCE AND CHEMICAL PROPERTIES

Among the fungi known to produce trichothecene mycotoxins, particularly T-2 toxin, are Fusarium sp. These organisms, like most fungi, are globally distributed, especially in agricultural foodstuffs such as cereal grains (e.g., corn, wheat, barley, sorghum, etc.).[5,8] Therefore, it is not surprising that T-2 and other trichothecene mycotoxins are found as natural contaminants of such crops. In nature, trichothecenes occur in mixtures rather than individually, and the concentration and composition of these mixtures at any given time in a particular food crop appears to be the result of the interaction between (1) environmental factors such as temperature and humidity, (2) chemical factors such as exhaustion of a particular nutrient, and (3) biological factors such as the enzymes of secondary metabolism (i.e., biochemical pathways induced by changes in chemical and physical conditions that restrict fungal growth), which determine the metabolites that are produced.[5]

Many different kinds of trichothecene mycotoxins have been isolated, but only six have been found naturally occurring in food crops.[9] The ones most frequently measured in agricultural commodities are T-2 toxin, DAS, nivalenol, and 4-deoxynivalenol.[5] Unfortunately, data are not available for estimating likely background concentrations for T-2 toxin and other trichothecene mycotoxins in the general environment (e.g., air, water, soil, and native vegetation). However, Watson et al.[6] do mention that T-2 toxin and other trichothecene mycotoxins were not found in samples of leaves or water taken from regions of Southeast Asia where "yellow rain" attacks were not reported. Such information suggests that environmental concentrations of trichothecene mycotoxins are typically low or absent.

Chemically, trichothecene mycotoxins are a group of spiroepoxy-containing sesquiterpenoid compounds. Ueno[9] divides these compounds into four groups (i.e., A through D) on the basis of their chemical characteristics and the fungi that produce them. Both T-2 toxin and DAS are among the trichothecene mycotoxins that are produced by F. tricinctum, F. sporotrichioides and a few other Fusarium, and belong to Group A. The basic chemical skeleton of the Group-A trichothecene mycotoxins is shown in Fig. 1; the substituted functional groups for T-2 toxin and DAS also are shown, along with their corresponding positions on the basic structure.



Trichothecene	Functional groups				
	R_1	R_2	R_3	R_4	R_5
T-2 toxin	OH	$OCOCH_3$	$OCOCH_3$	H	$OCOCH_2CH(CH_3)_2$
DAS	OH	$OCOCH_3$	$OCOCH_3$	H	H

Figure 1. Basic chemical skeleton of Group-A trichothecene mycotoxins. The epoxide ring, found essential for the toxicity of trichothecene compounds, and the substituted functional groups for T-2 toxin and diacetoxyscirpenol (DAS) are identified on the basic skeleton. Adapted from Ref. 5.

The toxicity of trichothecenes is related to the epoxide ring, which is sterically shielded. For example, results of research by Grove and Mortimer published in 1969 and unpublished findings by Grove in 1983 are discussed by the NRC Committee on Protection Against Mycotoxins[5] and indicate that the opening of the spiroepoxide ring of DAS and T-2 toxin yields similar products, all of which lack the toxicity of the parent compounds. Snyder and Fisk[10] also conclude from their review of the mycotoxin literature that destruction of the epoxide ring of trichothecene compounds leads to a total loss of toxic activity.

According to data on the physical properties of selected trichothecenes, T-2 toxin and DAS are white and colorless, respectively; however, HT-2 toxin is pale yellow.[5,10-11] Because Fusarium tricinctum can produce not only T-2 toxin, but also HT-2 and DAS,[8] it is conceivable that conditions favoring the production of large quantities of T-2 toxin by this fungus would also cause the fungus to synthesize some HT-2, which would impart a yellow color to a T-2 chemical munition.

The NRC Committee on Protection Against Mycotoxins[5] also reports that the solubilities of the trichothecene mycotoxins in different solvents are comparable. For

example, all are soluble in acetone, ethyl acetate, chloroform, acetonitrile, ethanol, and methanol, and relatively insoluble in water and petroleum ether. However, the solubility does vary for different trichothecene mycotoxins in benzene, toluene, and diethyl ether.

BEHAVIOR IN WATER

There is very little published information about the behavior of trichothecene mycotoxins in either waters, soils, or sediments. Also, very little information exist about the contamination of ground and surface waters by trichothecene mycotoxins or about the naturally occurring degradation products of these compounds. However, two recent laboratory studies described below provide data that (1) imply that T-2 toxin is relatively insoluble in water; (2) indicate that the stability of T-2 toxin in aqueous media is proportional to temperature, and at 22°C degradation should occur somewhat slowly over the course of a week with at least 80% of the compound remaining; and (3) suggest the possible breakdown products for T-2 toxin in water.

Wannemacher[12] describes an experiment in which the degree of T-2 toxin solubility in water at room temperature was determined. In that experiment, about 10 mg of T-2 toxin was first suspended in 1 mL distilled water (10,000 mg/L), vortexed (i.e., mixed by agitation) for 20 min, and then allowed to stand overnight at room temperature. After standing overnight, the suspension was centrifuged and an aliquot of solution was removed for analysis by immunoassay, which revealed a concentration of T-2 toxin in solution of approximately 0.5 mg/mL (500 mg/L). Although some T-2 toxin might have broken down over the course of one night, data from a study by Trusal,[13] to be discussed next, indicate that even at room temperature, the degradation process is slow and would not account for detection of such a small amount of T-2 toxin in solution. Therefore, insolubility of T-2 toxin is the likely reason so little T-2 toxin was detected.

Evidence from the study by Trusal[13] suggests that the stability of T-2 toxin in aqueous media will decrease with increasing temperature. In this study, T-2 toxin was first dissolved in Hank's balanced salt solution, which contains eight inorganic salts and D-glucose, and then stored for up to three weeks at temperatures of either 4, 22, or 37°C. The T-2 toxin was detected after 3 wk of storage at 4°C. However, the breakdown products of T-2 toxin, i.e., HT-2, T-2 triol, and T-2 tetraol, were identified (on the basis of comigration with known standards on thin-layer chromatography plates) as early as one day after the solution was stored at 37°C. At a temperature of 22°C, however, degradation of T-2 occurred somewhat slower; about 80% of the parent compound and

about 20% of its breakdown products were detected after one week. This would suggest that at environmental temperatures less than or equal to room temperature, breakdown does not occur fast enough over the course of 7 d to negate potential health concerns for military personnel.

TOXICITY OF BREAKDOWN PRODUCTS

Ohta et al.,[11] the NRC Committee on Protection Against Mycotoxins,[5] Yoshizawa et al.,[14] and Fan et al.[15] all report that some animals are capable of gradually reducing the toxicity of ingested T-2 toxin by first rapidly metabolizing it to the slightly less toxic HT-2 toxin, which is then transformed to the much less toxic T-2 tetraol through a number of additional steps. This metabolic transformation of T-2 toxin appears to be important for its elimination in feces and urine.[5] However, there is evidence to suggest that the possible breakdown products of T-2 toxin in natural waters may also be toxic if ingested. For example, Ohta et al.[11] state that in rats it is probable that T-2 toxin exerts its toxicity partly as HT-2 toxin. Consequently, should the breakdown products of T-2 toxin (HT-2, T-2 triol, and T-2 tetraol) be both stable and resuspendable in field water, it is possible that they too could impact the performance of exposed military personnel. Because the breakdown process and products of T-2 toxin in water and the relative toxicities of the products are not well defined, these issues need to be addressed by additional research and cannot be pursued further here. However, in the absence of any well-defined pathway of environmental degradation/detoxification for T-2 toxin, we assume T-2 toxin is environmentally persistent in soils, sediments, and waters.

DETECTION IN WATER

The field-water-quality test for the detection of the trichothecene mycotoxin T-2 being explored by the U.S. Army for possible incorporation into the M272 Chemical Agents Water Testing Kit[16] is based on the use of monoclonal antibodies (i.e., antibodies that exhibit specificity and high affinity for T-2 toxin).[17] This assay is now in advanced development and is designed to be a simple and very rapid test for determining, without laboratory facilities, whether or not T-2 toxin is present in field water. If the detection limit for T-2 toxin in water can be used to identify concentrations equal to and greater than those adopted as field-water-quality standards, then this immunochemical technique has attributes that make it suitable for field use.

The aforementioned immunochemical technique is colorimetric and can be considered a variation of the enzyme-linked immunosorbent assay (ELISA) used in laboratory analyses. Essentially, the test is a three-step process that uses one drop of water placed at the top of three layers of test material. As the water proceeds through the three layers of material, the following reactions occur: (1) monoclonal antibodies with a specificity and a high affinity for both T-2 and HT-2 toxin (antigens) combine with any T-2 or HT-2 toxin present in the water sample; (2) horseradish peroxidase (HRP) is then made to bind with any antigen-antibody complex that may be present; and (3) the resulting antigen-antibody-HRP compound is added to a mixture of hydrogen peroxide and 2,2'-azino-di-3-ethyl-benzthiazoline-6-sulfonate (ABTS), where hydrolysis of ABTS by HRP produces a blue-green product on the material upon which the reaction takes place. Color generation that is distinguishable from background by human vision occurs when T-2 concentrations in field water are at or above the detection limit.

In laboratory studies involving ELISA technology, calibrated instruments are used to measure color generation, and concentrations of T-2 toxin of 10^{-8} M or approximately 4.7 µg/L can be detected. However, the practical detection limit for T-2 toxin in field water by the present version of the field assay is 10^{-6} M or about 470 µg/L.[17] The lower sensitivity of the field assay can be attributed to the state of ELISA technology for field application. For example, calibrated instruments that can detect minute changes of color under controlled laboratory conditions will not be available in the field; consequently, the reduced sensitivity of the field assay results because the color change that is produced must be distinguishable from background by human vision and occur under less than ideal conditions.

PHARMACOKINETICS

Data from animal experiments, particularly those involving rodents and swine, indicate that trichothecene mycotoxins are rapidly absorbed from the gastrointestinal tract and then distributed by the blood relatively quickly to other organs, especially the liver, muscles, kidney, and stomach.[18-19] As mentioned earlier, some animals are capable of gradually reducing the toxicity of ingested T-2 toxin by first rapidly metabolizing it to the slightly less toxic HT-2 toxin, which is then transformed to the much less toxic T-2 tetraol through a number of additional steps.[5,11,14-15] This metabolic transformation of T-2 toxin appears to be important for its elimination in feces and urine; however, the significance of this metabolic modification with respect to elimination and

detoxification has not been well defined. Additionally, data from experiments with mice reported by Matsumoto et al.[18] indicate that single oral doses substantially lower than the LD50 may be eliminated rapidly; while data from experiments with swine published by Robison et al.[19] indicate that doses approaching the emetic dose may interfere with the elimination through the gastrointestinal tract. Furthermore, Kosuri et al.[20] concluded from studies with rats that clinical signs may not even develop until toxin doses are sufficient to overwhelm chemical pathways of detoxification and that for rats the dose of T-2 toxin that can overwhelm the detoxification process is probably close to the LD50.

HEALTH EFFECTS

Definitive data describing the relationship between human health effects and exposure to a specific mycotoxin has only been reported for the trichothecene mycotoxin, diacetoxyscirpenol (DAS or anguidine). The reason such data exist for DAS is because DAS has been studied in clinical trials to determine its efficacy as a chemotherapeutic agent for the treatment of cancer. Its selection for use in such trials was based on its activity in mice against two types of leukemia and a line of colon adenocarcinomas.[21] In the clinical trials described by Murphy et al.,[21] the most common dose-related toxic effects with observed thresholds in the cancer patients receiving DAS were nausea and vomiting; other effects also were noted, including (1) myelosuppression, (2) hypotension, (3) diarrhea, (4) central nervous system dysfunction, and (5) fever and chills.

T-2 toxin may also cause human health effects similar to the ones just described for DAS. For example, some of the symptoms, especially nausea and vomiting, were noted in persons in Japan and the Soviet Union during outbreaks of foodborne diseases that were attributed to the consumption of Fusarium-infected rice or grain; the most noted of these foodborne diseases is alimentary toxic aleukia (ATA).[22] Even though the etiology of foodborne diseases such as ATA in humans has never been established, it is thought that T-2 toxin played a prominent role in producing the observed adverse health effects.[9] Additionally, the NRC Committee on Protection Against Mycotoxins[5] noted that many of the symptoms of toxicity produced by DAS in cancer patients were among those reported to have been present in individuals claiming to be victims of military attacks of "yellow rain," and as mentioned earlier, T-2 toxin is considered to be the principal toxic ingredient of that possible military threat agent. Finally, experiments with animals under controlled laboratory conditions indicate that clinically, pathologically, and biochemically the toxicity of T-2 and DAS are similar and the mode of action is probably identical.

Table 1 summarizes LD50 (median lethal dose) data for T-2 toxin and DAS in mice, rats, guinea pigs, and swine that are relevant to ingestion. For the animal species and routes of administration shown, the ranges for the single dose LD50 for both T-2 toxin and DAS are nearly the same (i.e., 1.0 to 9.6 mg/kg body weight for T-2 toxin; 0.38 to 7.3 mg/kg body weight for DAS). Variation in the doses can be attributed to differences between species and routes of administration.

Also, in Table 1 the reported LD50 doses of T-2 toxin and DAS for the same animal species and route of administration are somewhat similar, generally differing only by a factor of up to three. Yet, a factor of three difference between the toxicity of T-2 toxin and DAS may even exceed the actual difference in toxicity between these compounds with respect to ingestion by humans. This is because the factor of three difference between the LD50s for T-2 toxin and DAS is for intravenous and not oral administration to swine. Although these animals possess anatomical and physiological properties similar to humans[33-35] and are considered to be an appropriate animal model for studying possible effects in humans from exposure to "yellow rain,"[36] accurate oral LD50 data for T-2 toxin and DAS are not available for swine because the T-2 toxin and DAS possess emetic properties that make such data hard to obtain[24,29] and make intravenous administration necessary to ensure uniform dosing.[33] In constrast, oral LD50 data for T-2 toxin and DAS do exist for rats, and intragastric LD50 data for the two compounds do exist for guinea pigs. The available oral LD50 data for rats for T-2 toxin and DAS indicate that T-2 toxin is twice as toxic as DAS when administered orally. The available intragastric LD50 data for guinea pigs for T-2 toxin and DAS indicate that the toxicity of the two compounds is nearly equal. Thus, these data for rats and guinea pigs when taken together suggest that with respect to ingestion by humans the difference in toxicity between T-2 toxin and DAS is probably less than a factor of three and may even be zero.

Furthermore, data concerning the minimum emetic dose for T-2 toxin for swine and monkeys and for DAS for swine and humans (see Table 2) also suggest that the inherent toxicity of these mycotoxins is similar. The minimum emetic dose for T-2 toxin and DAS ranges from a low value of 0.06 mg/kg body weight for DAS administered by rapid intravenous infusion to cancer patients to a high value for T-2 toxin of 1.0 to 2.0 mg/kg body weight administered by stomach tube to monkeys. Kosuri et al.[20] even mention that T-2 toxin was less toxic in rats when introduced intragastrically than intraintestinally and concluded that passage through the stomach may afford some protection against toxicity. One possible reason that passage of T-2 toxin through the stomach may afford some protection against toxicity is that some of the compound may be absorbed into the portal

Table 1. Summary of single dose LD50 values for T-2 toxin and diacetoxyscirpenol (DAS) in mice, rats, guinea pigs, and swine relevant to ingestion.

Trichothecene mycotoxin	Organism	Route of administration	LD50 (mg/kg)	Ref.
T-2 toxin	Guinea pig	Oral[a]	3.1	23
		Intragastric	1.0[b] to 5.3	24–25
	Mouse	Oral	4.8	26
		Intragastric	9.6[b]	25
	Rat	Oral	3.8	27–28
		Intragastric	7.0[b]	25
	Swine[c]	Intravenous[d]	1.2	29–30
Diacetoxy-scirpenol (DAS)	Guinea pig	Intragastric	1.0 to 2.0[b]	24
	Rat	Oral	7.3	27,31
	Swine[c]	Intravenous[d]	0.38	30,32

[a]Based on gastric intubation.

[b]Approximation.

[c]Swine possess anatomical and physiological properties similar to humans[33–35] and are considered an appropriate model for studying the possible effects in humans from exposure to "yellow rain."[36]

[d]Accurate LD50 data for swine are difficult to obtain by oral administration because of emetic properties of T-2 and DAS[24,29]; intravenous administration ensures uniform dosing.[33]

circulation and then undergo detoxification during first-pass metabolism through the liver prior to entering the general circulation.

The protection just mentioned may explain the difference of more than a factor of 10 between the intragastric daily dose of T-2 toxin observed to cause emesis in monkeys and the intravenous daily dose of DAS observed to cause emesis in cancer patients. Additionally, the time of onset of nausea and vomiting in cancer patients receiving the

Table 2. Minimum emetic dose relevant to ingestion for T-2 toxin in swine and monkeys and for diacetoxyscirpenol (DAS) in swine and humans.

Trichothecene mycotoxin	Organism[a]	Route of Administration	Emetic dose (mg/kg)	Ref.
T-2 toxin	Swine[b]	Intragastric (gavage tube)[c]	0.4[d]	19
		Oral[c]	0.1[d]	37
		Intravenous[c]	0.6[e]	34
	Monkey	Intragastric (stomach tube)[f]	1.0 to 2.0[g]	38
Diacetoxy-scirpenol (DAS)	Swine[b]	Intravenous[c]	0.5[h]	33
		Oral[c]	0.1[d]	37
	Humans[i]	Intravenous[j]	0.06[k]	21

[a]Some laboratory animals, rodents in particular (e.g., guinea pig), do not have the capability (reflex) to vomit[24,25]; consequently, this effect cannot be measured in these organisms.

[b]Swine possess anatomical and physiological properties similar to humans[33-35] and are considered an appropriate model for studying the possible effects in humans of "yellow rain." [36]

[c]Single dose.

[d]Highest dose tolerated before vomiting was induced.

[e]Vomiting was observed.

[f]Daily dose.

[g]Vomiting was observed in male monkeys within 3 h of dosing on second day of administration.

[h]Vomiting was observed and dose was fatal to one of four pigs.

[i]Cancer patients.

[j]Rapid intravenous infusion (i.e., DAS was administered over 30 to 60 min).

[k]Based on 2.4 mg/m^2 per day[21] and a conversion factor of 1.8 m^2/70-kg individual. Time of onset for nausea and vomiting not specified for a daily dose of 2.4 mg/m^2 (0.06 mg/kg) but at 5 mg/m^2 (0.13 mg/kg) per day severe nausea and vomiting developed after only one to three doses in some individuals.[21]

dose of 0.06 mg/kg (2.4 mg/m^2) per day was not identified, although at a dose of 0.13 mg/kg (5.0 mg/m^2) per day, severe nausea and vomiting developed after only one to three doses in some individuals.[21] Additionally, cancer patients probably represent sensitive members of the population.

In addition to producing the physiological effects already mentioned, T-2 toxin can be an extremely potent skin irritant.[5,20] Such irritation in the oral cavity and intestinal tract when the mycotoxin is present in food or water may play a role in feed or water refusal by exposed organisms.[8] For example, Burmeister et al.[39] showed that mice will reduce their daily consumption of drinking water in response to the presence of T-2 or DAS in their water supply. In this study, the concentration of T-2 toxin or DAS in the drinking water of mice ranged from 2 to 40 mg/L. At a concentration of 2 mg/L of T-2 or DAS in drinking water, the mice reduced their daily consumption of the water by 29 and 16%, respectively. When T-2 toxin or DAS was present in the water at a concentration of 40 mg/L, the mice reduced their daily intake of the water by the substantial margin of 80 and 66%, respectively. All results were found to be significant statistically compared with controls (least significant difference at 5% level, 0.89).

MECHANISM OF ACTION

Trichothecene mycotoxins are among the most potent inhibitors of protein synthesis.[40] In fact, T-2 toxin and DAS exhibit similar potent activity in eukaryotic cells.[41] Thompson and Wannemacher[42] indicate that the minimum effective dose of T-2 toxin for producing inhibition of protein synthesis in tissue culture cells (Vero cells) is 3 ng/mL, and that 10 to 20 ng/mL of T-2 toxin is sufficient to cause 50% inhibition of protein synthesis in such cells. Therefore, it is likely that the toxic effects produced by T-2 toxin are related to its ability to inhibit protein synthesis. For example, T-2 toxin and other trichothecenes have been shown to exert their greatest impact systemically in tissues with large complements of rapidly dividing cells, such as (1) the digestive tract, (2) the hematopoietic and immune tissues, (3) the reproductive organs, and (4) the cardiovascular system. Thus, the cytotoxicity of T-2 toxin has been described in the literature as being radiomimetic.[5,43]

PROLONGED FEEDING STUDIES OF T-2 TOXIN TO LABORATORY ANIMALS

Observed effects in prolonged feeding studies of T-2 toxin to mice, rats, and monkeys include gastric lesions and suppression of the immune system (see Table 3).

Table 3. Results from prolonged feeding studies of T-2 toxin to laboratory animals.

Organism	Administration Route	Administration Period	Estimated daily dose (mg/kg)	Observed Effects	Ref.
Mice	Oral[a]	12 months	2.5[b]	Gastric lesions[c]	43
Rats	Oral[d]	4 wk	0.38[e]	Negligible	43
Monkeys	Intragastric[f]	4 to 5 wk	0.1	Fatal within 5 d or immune suppression[g]	44

[a]DDD female mice given feeds containing 10 μg of T-2/g of food.

[b]Daily dose estimated on the basis of a rough approximation of the daily food intake for mice of 250 g of feed/kg of body weight.[45]

[c]Lesions appeared within 13 weeks and were observed consistently for the remainder of the 12-month exposure period; however, the effects subsided 3 months after the experiment ended.

[d]Wistar rats given feeds containing 5 μg of T-2/g of food.

[e]Daily dose reported to cause negligible effects (i.e., gastric lesions were observed at daily doses two and three times greater) and estimated on the basis of a rough approximation for the daily food intake for rats of 75 g of feed/kg of body weight.[45]

[f]Seven male rhesus monkeys given the equivalent of 0.1 mg of T-2 toxin/kg of body weight in milk by stomach tube.

[g]Three out of seven monkeys developed complications including nausea, vomiting, hemorrhage, and respiratory infection, and died within about 5 d of the beginning of the experiment. The four surviving animals that received 0.1 mg/kg daily over four to five weeks only suffered suppression of the immune system.

However, these effects develop over time (e.g., after about 5 d of exposure) and appear to be reversible once exposure has ceased. For example, in a study of seven monkeys, Jagadeesan et al.[44] found that T-2 toxin, administered in milk by stomach tube over 4 to 5 wk at a daily rate of 0.1 mg/kg of animal body weight, suppressed the immune system of the 4 surviving animals. (Three of the monkeys tested developed complications including nausea, vomiting, hemorrhage, and respiratory infection, and died within about 5 d of the beginning of the experiment.) The immunological effects seemed to be reversed in the animals after a period of 5 months without exposure to T-2 toxin, which suggests

that depression of the immune system may not be permanent. Furthermore, Ohtsubo and Saito[43] conclude from a review of data from prolonged feeding studies of trichothecene mycotoxins to laboratory animals that it is unlikely that chronic trichothecene toxicosis occurs in humans.

CARCINOGENICITY, MUTAGENICITY, AND TERATOGENICITY

Data obtained by Marasas et al.[46] from long-term feeding studies with animals (e.g., albino rats and rainbow trout) indicate that there is no evidence that trichothecene mycotoxins are carcinogenic. However, few long-term feeding studies have been completed, and so further work is needed in this area to more thoroughly resolve this issue.[5] According to the review of the chronic effects data for trichothecene mycotoxins performed by the NRC Committee on Protection Against Mycotoxins,[5] none of the trichothecenes have tested positive for mutagenicity, but T-2 toxin has been shown to be teratogenic in studies involving its effect on embryonic and fetal development in mice following its administration intraperitoneally in single doses between 0.5 and 1.5 mg/kg of body weight. However, the teratogenic risk to human populations following chronic ingestion of environmental concentrations of T-2 toxin cannot be extrapolated from such limited studies identifying the teratogenic toxicity of T-2 toxin in mice.

DEVELOPMENT OF MAXIMUM PERMISSIBLE CONCENTRATIONS (MPCs) FOR CONSIDERATION AS INTERIM FIELD-WATER-QUALITY STANDARDS

The available data concerning the biochemistry and toxicology of T-2 and DAS suggests that these two mycotoxins are comparable with respect to their toxic properties. Accordingly, the human dose-response data for DAS administered to cancer patients is employed to derive recommendations for field-water-quality standards for T-2 toxin. However, dose-response data for the toxicity of T-2 toxin in animals are also evaluated with respect to extrapolation to humans to support such recommendations. In summary, the DAS dose-response data for cancer patients are applicable for all of the following reasons: (1) the chemical structures of T-2 and DAS differ only slightly, (2) the LD50 and minimum emetic doses relevant to ingestion for T-2 toxin and DAS for animals and humans indicate that the inherent toxicities of these two mycotoxins are comparable, (3) human toxicity data concerning trichothecene toxicosis are preferred to animal data in order to minimize uncertainties associated with extrapolation from animal to man, and

(4) cancer patients, because of their physiological stress, represent sensitive members of the population; consequently, a field-water-quality standard based on their responses will have an implicit margin of safety for healthy individuals.

Because DAS was administered intravenously to cancer patients in clinical trials and these are the only human data available for use in developing field-water-quality standards for T-2 toxin, the assumption is made that intravenous doses of the trichothecene mycotoxins are equivalent to doses from ingestion for humans. Moreover, research results summarized by the NRC Committee on Protection Against Mycotoxins[5] indicate that health effects such as nausea, vomiting, and lassitude, which are effects that can be considered performance degrading in military personnel, appear to develop regardless of the route of exposure. However, toxicity data presented in Table 2 concerning emetic doses of T-2 toxin and DAS administered both intravenously and orally to swine suggest that intravenously administered doses of these trichothecene mycotoxins might actually be more toxic than orally administered ones. As discussed earlier, such differences in toxicity between intravenous and oral doses might occur because passage through the stomach could provide some protection against toxicity.[20] On the basis of such information, the assumption that intravenous and oral doses are equivalent might incorporate an additional amount of conservatism into the resulting field-water-quality standards.

Another assumption that is made is that absorption from the gastrointestinal tract is virtually complete because metabolic studies indicate that trichothecene mycotoxins are rapidly absorbed from the gastrointestinal tract. For example, tissue distribution experiments of orally administered T-2 toxin to rats and mice show that absorption is rapid and the toxin is quickly distributed to many organs, which probably accounts for the onset of cellular impairment beginning shortly after ingestion, particularly in the stomach and small intestine.[18] However, in the experiments with mice, it was also noted by these researchers that T-2 toxin did not accumulate in the tissues, and, after 3 d, 68% of the T-2 toxin that was orally administered had been eliminated in the feces (51%) and urine (17%). Matsumoto et al.[18] also showed that 27% of the dose of T-2 toxin orally administered to mice was quickly distributed to the liver, and that 30 min after administration the bile contained a considerable fraction of the dose, which they concluded to be the most likely pathway by which the toxin is eliminated from the liver. Nevertheless, there is evidence from this study with mice to suggest that once the toxin (or its degradation products) is eliminated into the intestine through the bilial excretion system some of it is reabsorbed and redistributed.

In the study involving intravenous administration of DAS to human cancer patients reported by Murhpy et al.,[21] no drug-related toxicity was observed in any cancer patient

receiving a DAS dose by rapid intravenous infusion (administered over 30 to 60 min) of less than 2.4 mg/m^2 (0.062 mg/kg of body weight[a]) per day for 5 d. However, at that dose, one patient was observed to suffer mild nausea and vomiting. Additionally, in clinical trials involving DAS administration to human cancer patients by intravenous "push" reported by Goodwin et al.,[47] 10 out of 24 patients experienced some nausea and vomiting at a dose rate between 0.2 mg/m^2 (0.005 mg/kg of body weight) and 2.4 mg/m^2 (0.062 mg/kg of body weight) per day for 5 d. The initial dose rate in the clinical trial reported by Murphy et al.[21] was 0.1 mg/m^2 (0.0026 mg/kg of body weight) per day for 5 d, and at this dose rate no health effects were observed.

Unfortunately, the dose-response data just described for DAS for cancer patients do not rule out the possibility that the no-effect daily dose of the compound administered for 5 d by rapid intravenous infusion might be one that actually is greater than that reported to produce no health effects (0.0026 mg/kg) but lower than those doses reported to cause adverse health effects (0.005 to 0.062 mg/kg). However, it does not seem appropriate to speculate further about the existence or magnitude of such a dose for use as the no-effect level for T-2 toxin because a relatively steep slope for the dose-response relationship for T-2 toxin is suggested by data from an acute toxicity study by Chan and Gentry[48] that involved single-dose administrations of T-2 toxin intramuscularly to rats (e.g., LD10 = 0.70 mg/kg and LD90 = 1.03 mg/kg) and rabbits (e.g., LD10 = 0.73 mg/kg and LD90 = 1.64 mg/kg). More specifically, the possibility that a steep slope is associated with the dose-response relationship for T-2 toxin for ingestion in water over time by humans means that significant health effects might result from any small increase in dose above a no-effect level. Consequently, any dose of DAS considered to represent the no-effect level for T-2 toxin should not be selected arbitrarily. For these reasons and because no health effects were reported to be associated with rapid intravenous infusion of DAS at a rate of 0.0026 mg/kg per day for 5 d, this level of DAS is considered to be a sensible one to use for deriving interim field-water-quality standards for T-2 toxin for an exposure period lasting up to 7 d. Thus, the interim field-water-quality standard recommended for T-2 toxin for 70-kg military personnel drinking up to 5 L/d of field water for a period lasting up to 7 d is calculated as

$$0.0026 \text{ mg/(kg} \cdot \text{d)} \cdot 70\text{-kg person} \cdot 5 \text{ d/7 d} \cdot \text{d/5 L} = 0.026 \text{ mg/L (26 mg/L)}. \quad (1)$$

[a]Based on a conversion factor of 1.8 m^2 of body-surface area per 70-kg individual.

Similarly, the interim field-water-quality standard recommended for T-2 toxin for 70-kg military personnel consuming up to 15 L/d of field water for a period lasting up to 7 d is calculated as

$$0.0026 \text{ mg/(kg} \cdot \text{d)} \cdot 70\text{-kg person} \cdot 5 \text{ d/7 d} \cdot \text{d/15 L} = 0.0087 \text{ mg/L (8.7 } \mu\text{g/L)}. \quad (2)$$

Additional support for using the daily dose rate of DAS of 0.0026 mg/(kg • d) for 5 d as the basis for recommending military field-water-quality standards for exposure lasting up to 7 d comes from comparing this dose with those for humans extrapolated from (1) the minimum emetic doses in animals for T-2 toxin and DAS shown in Table 2 and (2) the doses of T-2 toxin administered to laboratory animals during prolonged feeding studies shown in Table 3. The extrapolation to humans from the animal data is made by using safety factors of 10 and 100 as boundary conditions.

The safety factors of 10 and 100 have been recommended, to account for uncertainties associated with extrapolating from (1) studies of prolonged ingestion by average humans to those more sensitive individuals in the population, and from (2) long-term feeding experiments with laboratory animals to average humans, respectively.[49,50] Although the animal data concerning minimum emetic doses for T-2 toxin and DAS involve administration of one single dose or a single dose administered daily for two days (i.e., in monkeys), safety factors of 10 and 100 are reasonable because (1) the performance-degrading effects of interest (e.g., nausea, vomiting, lassitude, etc.) are acute and develop rapidly; (2) trichothecene mycotoxins seem to be metabolized quickly and do not appear to be cumulative poisons; and (3) military personnel are not expected to be exposed to field water contaminated with T-2 toxin for more than 7 d.

Application of the safety factors of 10 and 100 to the minimum emetic dose for T-2 toxin administered as a single dose orally or intragastrically in swine yields a range of extrapolated values for humans of 0.001 to 0.04 mg/kg. The range of values for the human emetic dose for T-2 toxin extrapolated from data for swine administered a single intravenous dose of T-2 toxin is 0.006 to 0.06 mg/kg. Application of the safety factors to the minimum emetic dose for T-2 toxin administered intragastrically as a daily dose in monkeys results in extrapolated values for humans ranging from 0.01 to 0.2 mg/kg. Finally, applying the safety factors to the minimum emetic dose for DAS administered intravenously as a single dose in swine results in extrapolated values for humans ranging from 0.005 to 0.05 mg/kg. The minimum values of the dose ranges extrapolated from the swine data for both T-2 toxin and DAS (i.e., 0.001, 0.006, and 0.005 mg/kg) are quite similar to the daily dose rate of DAS in humans that we use as the basis for our

recommendations for military field-water-quality standards for T-2 toxin (i.e., about 0.003 mg/kg). The daily dose rate of DAS in humans is one-fourth to one-third of the minimum value of the dose range extrapolated from the monkey data for T-2. This difference could be associated with the route of administration (i.e., intragastric for monkeys and intravenous for humans), especially if administration through the stomach does offer some protection against toxicity in primates and humans. Therefore, these comparisons reveal that the dose rate of DAS that was reported to produce no adverse health effects in human cancer patients after 5 d of intravenous administration is a reasonable, albeit conservative, one to use for developing field-water-quality standards for military personnel. However, it may not be too conservative because dose-response data reported by Goodwin et al.[47] for cancer patients administered DAS by intravenous "push" in a clinical trial indicate that the daily dose for producing nausea and vomiting could range from a value as low as 0.2 mg/m^2 to a value equal to 2.4 mg/m^2 (i.e., 0.005 to 0.06 mg/kg).

Moreover, the minimum values of the extrapolated dose ranges for humans that result from the application of the safety factors of 10 and 100 to the data from prolonged feeding studies shown in Table 3 compare favorably with the daily dose rate of DAS in humans upon which we base our recommendations for military field-water-quality standards. For example, the daily dose rate of DAS for cancer patients of about 0.003 mg/kg is quite similar to the minimum value of the dose range extrapolated from the data for rats (about 0.004 mg/kg per day) and monkeys (about 0.001 mg/kg per day) and within an order of magnitude of the minimum of the dose range for mice (about 0.025 mg/kg per day). The order of magnitude difference between the human data for DAS and the extrapolated data from mice for T-2 is consistent with the fact that the LD50 for T-2 toxin is higher for mice than for other laboratory animals (see Table 1); consequently, mice apparently can tolerate higher doses of T-2 toxin before developing any signs of toxicity.

Although the interim field-water-quality standards recommended for T-2 toxin for up to 7 d of exposure (derived from a no-effect daily dose of DAS of 0.0026 mg/kg for 5 d) are not likely to produce any performance-degrading health effects in military personnel, as mentioned before, such standards may err somewhat on the side of safety. The possibility that the health of the cancer patients in the clinical trials might be compromised by their disease is regarded as the most likely factor that could contribute to such an underestimate. This would make these patients susceptible to the toxicity of DAS at doses that are lower than those at which healthy individuals, such as military personnel, might be affected. For example, Murphy et al.[21] report that daily doses of DAS greater

than 3 mg/m^2 (0.077 mg/kg) that were administered to cancer patients for 5 d by rapid intravenous infusion produced the most severe symptoms, including moderately severe gastrointestinal toxicity (e.g. nausea, vomiting, and diarrhea), in patients suffering from liver metastases, elevated bilirubin levels, or liver function abnormalities. Furthermore, daily doses of DAS equal to 0.077 mg/kg that were administered to cancer patients by rapid intravenous infusion for 5 d, only eliminated the most severe toxic reactions in the patients with liver abnormalities. Both these patients and the ones without liver abnormalities that were administered this dose, still experienced at least some nausea and vomiting. Finally, one cancer patient even experienced mild nausea and vomiting as a result of a daily dose of DAS equal to 2.4 mg/m^2 (0.062 mg/kg) that was administered by rapid intravenous infusion for 5 d. Notwithstanding, these data do not unequivocally rule out the possibility that even some healthy individuals administered such doses would suffer some symptoms. The data also do not eliminate the possibility that even the mildest symptoms would be performance degrading for some military personnel. In fact, there is evidence from the data regarding the adverse health effects associated with exposure to radioactivity that healthy people and cancer patients will respond to similar doses in the same physiological manner.[51] Furthermore, for these reasons and also because the dose-response relationship for T-2 toxin is potentially steep, none of the previously described doses of DAS were considered suitable for use in developing field-water-quality standards for T-2 toxin.

To address potential concerns that the above assessment may be too conservative, we offer the following alternative assessment with some noted reservations. If a daily dose of DAS as high as 0.077 mg/kg administered by rapid intravenous infusion to cancer patients for 5 d were considered for use in developing field-water-quality standards for military personnel, one assumption must change. This assumption is that such a daily dose of DAS would produce no symptoms, or such mild symptoms that performance would not be significantly impacted, in a population of healthy military personnel. Accordingly, on the basis of such a dose, and substituting 0.077 mg/(kg•d) for 0.0026 mg/(kg•d) in Eq. 1, the concentration in field water for T-2 toxin for a 5 L/d consumption rate and exposure not exceeding 7 d is calculated as 0.77 mg/L. Similarly, substituting 0.077 mg/(kg•d) for 0.0026 mg/(kg•d) in Eq. 2, the concentration in field water for T-2 toxin for a 15 L/d consumption rate and exposure not exceeding 7 d is calculated as 0.26 mg/L. These concentrations in field water are about 30 times larger than the ones being recommended for use as interim field-water-quality standards for T-2 toxin. However, on the basis of the data available, especially a potentially steep dose-response relationship for T-2 toxin, the assumption upon which these higher concentrations are

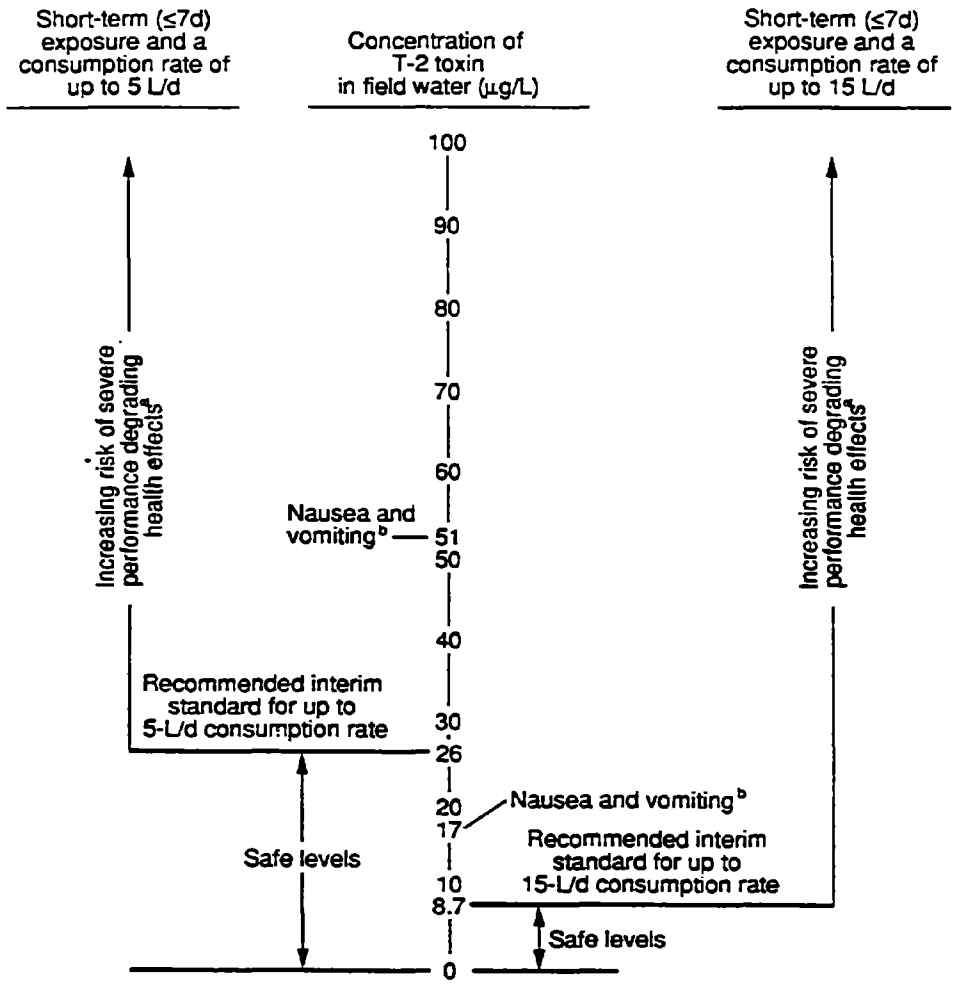
based may not be a prudent one, and the lower concentrations recommended as interim field-water-quality standards may not include a margin of safety that even approaches a factor of 30.

RISK ASSESSMENT

Figure 2 is a visual guide for assessing the impact of concentrations of T-2 toxin that exceed the recommended interim standards. The figure shows that the performance-degrading health effects most likely to be experienced at concentrations above the standards are nausea and vomiting. On the basis of data from clinical trials using DAS as a chemotherapeutic agent to treat cancer patients, the mildest symptoms might be associated with concentrations of T-2 toxin just above the recommended standards, while the most severe symptoms probably are associated with concentrations more than 30 times greater than the recommended standards.

SUMMARY AND CONCLUSIONS

The published health-effects data for animals and humans for the trichothecene mycotoxins T-2 and DAS suggest that the safest concentrations of T-2 toxin to recommend for use as interim field-water-quality standards for military personnel for drinking-water consumption rates up to 5 and 15 L/d for a period lasting up to 7 d should be based on the daily dose of DAS that produced no adverse health effects in cancer patients after 5 d of intravenous administration. This daily dose is 0.0026 mg/kg. However, such a dose includes an implicit margin of safety because of the ill health of cancer patients and the possibility that DAS administered intravenously is possibly toxic at lower concentrations than DAS administered orally. Nevertheless, on the basis of the available data, especially the possibility that the dose-response relationship for T-2 toxin is relatively steep, it is not considered prudent to advocate that a higher daily dose of DAS be used to derive interim field-water-quality standards for T-2 toxin.



[a]Potentially performance-degrading health effects may include nausea, vomiting, diarrhea, generalized burning erythema, and mental confusion according to studies with DAS in clinical trials.[21,47]

[b]Based on lowest daily intravenous "push" dose of DAS reported by Goodwin et al.[47] to produce nausea and vomiting in cancer patients. Most severe health effects, including gastrointestinal problems, were reported in cancer patients administered a daily dose of DAS by rapid intravenous infusion for 5 d that was about 30 times greater than the one used to calculate the standards. Therefore, concentrations of T-2 toxin that are 30 times greater than the recommended interim field-water-quality standards are expected to produce the most severe toxic symptoms.

Figure 2. Health-effects summary for T-2 toxin in field water (based on administration of DAS in clinical trials to cancer patients).

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CHAPTER 6. LEWISITE

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INTRODUCTION

Lewisite is the organic trivalent-arsenic compound, 2-chlorovinyldichloroarsine.[1,2] This threat agent is not only a potent vesicant (i.e., blister agent), but also a lung irritant and systemic poison.[3,4] These toxic effects have been attributed to the fact that lewisite is a lipid-soluble compound and as such the trivalent arsenic it contains not only can enter the skin rapidly and cause painful localized blistering, but also can easily penetrate the skin and consequently exert its toxic action systemically.[2,5] Trivalent arsenic (As) in its inorganic form (e.g., arsenious oxide) ordinarily would not be acutely injurious to tissue because it is not lipid-soluble like lewisite; however, its intimate, prolonged contact with human skin may produce erythema and vesication eventually.[5]

Because trivalent arsenic is considered the component of lewisite that is principally responsible for its vesicant and systemic toxicity at the cellular level,[2,6] arsenic-based field-water-quality standards for lewisite (i.e., standards expressed in terms of the arsenic fraction of lewisite) will be derived. Furthermore, such arsenic-based standards for lewisite are practical because, as will be discussed, the water-quality test for lewisite currently used by the military does not detect lewisite directly,[7] instead the presence of lewisite in water is based on detection of its arsenic component.

No human data could be found concerning the toxicity of lewisite via the oral route of exposure. A review of the literature concerning lewisite did reveal limited toxicity data from three different studies with laboratory animals. One of these studies was a long-term ingestion experiment that was reported in 1941 by Leitch et al.[8] This research focused specifically on evaluating the toxicity of the daily ingestion by rats of water containing concentrations of either 10 or 16 ppm (mg/L) of lewisite over a prolonged period of time (133 d). The second study concerning the toxicity of ingested lewisite was reported in 1987 by Hackett et al.[9] The purpose of this study was to determine the toxic response to lewisite of pregnant rats and rabbits and their conceptuses following daily, intragastric administration to the maternal animals during the period of gestation that encompasses major organogenesis (10 or 14 daily doses for the rat and rabbit,

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respectively). The third and most recent study was performed by Sasser et al.[10] at Pacific Northwest Laboratory under contract to the U.S. Army Biomedical Research and Development Laboratory at Fort Detrick. The objective of this research was to evaluate the subchronic toxicity of lewisite in rats.

The data from the three studies will be evaluated for use in establishing arsenic-based maximum permissible concentrations (MPCs) for lewisite in water that should protect military personnel against performance-degrading health effects. Recommendations for interim arsenic-based field-water-quality standards for lewisite will then be made based on this evaluation. Descriptions of (1) the pertinent chemical and physical properties of lewisite, (2) its behavior and detection in water, (3) its mechanism of action, and (4) the health effects that could result from its ingestion at doses above safe levels also are presented.

CHEMICAL AND PHYSICAL PROPERTIES

Table 1 contains selected chemical and physical properties for lewisite that were summarized by Hackett et al.[9] from data compiled by Rosenblatt et al.[11] Lewisite contains both the trans and cis isomers of 2-chlorovinyl-dichloroarsine, however, the trans isomer predominates (>90% by weight).[9,11] Nevertheless, according to research from the 1940's cited by Hackett et al.[9] and Rosenblatt et al.,[11] the trans and cis isomers appear to be equally toxic. Additionally, pure lewisite is a colorless, odorless substance, but usually it contains a very small amount of impurities that can give it a brownish color and a geranium-like smell.[1]

BEHAVIOR IN WATER

Ordinarily, lewisite will dissolve very slowly in water; however, as it dissolves it does hydrolyze rapidly (see Table 1) forming hydrochloric acid (HCl) and lewisite oxide (Cl–CH=CH–AsO).[12,13] Because lewisite is actually an oily liquid at ordinary temperatures and pressures, when it comes in contact with water it can form a surface film and globules that can fall to the bottom of calm waters and accumulate in sediments.[12] Additionally, Waters and Williams[14] state that upon treatment with water, lewisite can yield a strong-acid solution and a sticky gum that is a mixture of a polymerized oxide and unchanged lewisite. Notwithstanding, Bouder[13] reports that when lewisite is introduced into large volumes of water (about 25 volumes in excess of the volume of lewisite) and then mixed, it will hydrolyze rapidly.

Table 1. Selected chemical and physical data for lewisite (2-chlorovinyldichloroarsine).[a]

Structural formula:	Cl–CH=CH–$AsCl_2$
Molecular weight:	207.3 g
Solubility in water:	Very slightly soluble
Hydrolysis rate:	Rapid
Hydrolysis products:	Chlorovinyl arsenous oxide, HCl (in acid solutions) Acetylene, sodium arsenate (in alkaline solutions)

[a] Summarized by Hackett et al.[9] from data compiled by Rosenblatt et al. [11]

DETECTION IN WATER

The M272 Chemical Agents Water Testing Kit now being introduced by the U.S. Army contains a test for lewisite.[7] The test involves converting the arsenic in lewisite to arsine using zinc in an acid solution. The gas bubbles that are created by the reaction pass through white beads that will change to a yellow or brown color if there is a concentration of lewisite equal to or greater than 2 mg/L. The beads remain white if the concentration of lewisite is less than 2 mg/L. However, the sensitivity of this test needs to be improved because, at the sensitivity just described, it does not even detect arsenic produced from lewisite at concentrations that are recommended as short-term standards for total inorganic arsenic in Chapter 7 of Part 1 of this volume (i.e., arsenic concentrations of 0.3 and 0.1 mg/L for 5 and 15 L/d consumption rates, respectively, for up to 7 d).[15] Additionally, lewisite appears to be more toxic than inorganic trivalent arsenic, as will be discussed shortly, and so recommended interim standards for lewisite arsenic will be lower than those just mentioned for total inorganic arsenic.

Odor may be a method for the detection of lewisite; our review of the literature revealed one report that stated that the smallest concentration of lewisite found to be capable of producing a perceptible odor in water was between 100 and 300 ppb (µg/L).[16] However, such odor detection limits for lewisite in water will require confirmation because the available data are very limited.

MECHANISM OF ACTION AND HEALTH EFFECTS

In Chapter 7 of Part 1 of this volume, the affinity of trivalent arsenic for sulfhydryl groups and the chemical binding that results were mentioned as the mechanism by

which trivalent arsenic can inactivate the functional activities of cells.[15] Similarly, the trivalent arsenic in the lewisite compound inactivates the functional activities of cells by binding to sulfhydryl-containing proteins, especially enzymes.[17,18] Specifically, lewisite kills cells primarily by inhibiting pyruvate oxidation, which is a critical step in carbohydrate metabolism; the biochemical process by which cells are supplied with energy.[5,19] This inhibition appears to result because the enzymes responsible for oxidation of pyruvate contain sulfhydryl groups and the trivalent-arsenic of lewisite easily penetrates the cells and reacts with two of the sulfhydryl groups that are close together on an enzyme to form a relatively stable, cyclic thioarsenite.[20,21]

Although the process by which inorganic trivalent arsenic and the trivalent arsenic of lewisite inhibit cellular function is virtually the same, a study by Inns et al.[22] comparing the intravenous LD50 (median lethal dose) in rabbits for sodium arsenite ($NaAsO_2$; LD50 = 7.6 mg/kg) with that for lewisite (LD50 = 1.8 mg/kg) reveals that on the basis of trivalent arsenic content the former is 6.5 times less toxic than the latter. These researchers also observed other differences between the two intravenously administered compounds that included signs of poisoning, times to death, and tissue arsenic content. Additionally, gross and histological studies confirmed severe pulmonary damage and biliary epithelial necrosis in lewisite-dosed rabbits, but such injury was not found in those animals given sodium arsenite. The authors concluded from the findings that the toxic action of lewisite was different from that of inorganic trivalent arsenic. They also conjectured that the observed difference in toxic action and arsenic distribution in tissue between the two compounds might be related to the greater lipid solubility of lewisite and its vesicant action. These two properties of lewisite will facilitate its rapid permeation into cells where the trivalent arsenic will react with sulfhydryl proteins to inhibit cellular functions.

Other data compiled by Hogan and Eagle[23] show that the toxicity of arsenicals is a function of the degree to which they are bound in the tissues and their rate of excretion. Consequently, the most toxic arsenical compounds are bound strongly and excreted slowly. According to a review of the literature by Buchanan,[4] lewisite forms more stable compounds with sulfhydryl-containing proteins than those obtained with inorganic trivalent arsenic (e.g., sodium arsenite). Moreover, experiments by Barron et al.[24] showed that lewisite also possesses a greater affinity for the sulfhydryl groups of cellular enzymes than other organic trivalent arsenicals and inorganic arsenite. Accordingly, inorganic trivalent-arsenic compounds (e.g., sodium arsenite) apparently cannot enter cells as easily as lewisite and do not have as great an affinity for the sulfhydryl groups on cellular proteins. Thus, the tissue distribution for inorganic trivalent-arsenic

compounds should differ from that for lewisite, and inorganic trivalent-arsenic compounds probably are eliminated more rapidly. Such behavior by inorganic trivalent-arsenic compounds would help explain why they are not as toxic as lewisite.

The greater affinity of lewisite for the sulfhydryl enzymes responsible for critical cellular functions has been attributed to its vinyl (CH_2=CH–) group.[24] The vinyl group in the lewisite molecule might also be responsible for the potent vesicant action of the compound; the vesicant action has been attributed to the organic chemical structure of lewisite.[2] Although the toxicity of the vinyl group has not been reported, Waters and Williams[14] indicate that vesicant action is not a function of the $AsCl_2$ group of the compound. They found that carefully prepared solutions of lewisite oxides (–AsO) or dihydroxides (–As[OH]$_2$) were equally as potent as lewisite with respect to vesicant action. Additionally, the toxicity of lewisite and perhaps its vesicant action as well depend on the presence of the trivalent-arsenic atom because when pentavalent arsenic was substituted for the trivalent arsenic by converting lewisite to 2-chlorovinylarsonic acid the latter molecule was not as toxic as the former.[2]

As noted earlier, Waters and Williams[14] determined that the vesicant action of lewisite oxide, which is produced in water as a result of the rapid hydrolysis of lewisite, appears to be identical to that of the parent compound. Rosenblatt et al.[11] further assume that the toxicities of both lewisite and lewisite oxide are similar and because the toxicity literature addresses lewisite primarily, the two compounds can be considered identical toxicologically. In fact, it has been suggested by Cameron et al.[2] and Graham et al.[25] that the lewisite transported systemically from the skin in the circulation is actually the hydrolyzed form, lewisite arsenoxide. Additionally, Peters et al.[5] showed that at low concentrations the oxide of lewisite can inhibit the activity of sulfhydryl enzymes that are critical for cellular function. However, research by Price and von Limbach[26] involving fish suggests the possibility that lewisite and its hydrolysis products may undergo additional chemical changes in water over extended periods of time and the resulting compounds will be less toxic than the lewisite or its hydrolysis products. For example, in a series of experiments described by these researchers, freshly prepared, highly concentrated, aqueous solutions of lewisite were introduced into four different aerated aquaria so that the initial concentration in each tank would be 5 mg/L in 50 L of water. Five bluegills were then introduced into each tank after a certain period of time elapsed: i.e., 3 h, 1 d, 7 d, and 50 d. The fish in the first two tanks died within an average time of about 2 h (0.1 d). The five bluegills placed into the third tank died within an average time of about 4 h (0.17 d). The fish introduced into the fourth tank remained alive even after 30 d had passed. The authors concluded that the lewisite probably underwent oxidation

and the products of this reaction were less toxic than the parent compound. However, the oxidation process was quite slow, requiring several weeks to occur, even though aeration was present.

Acting as a systemic poison, lewisite can produce pulmonary edema, diarrhea, restlessness, weakness, subnormal temperature, and low blood pressure.[3] However, lewisite is primarily a capillary poison, and vascular damage is partly responsible for effects such as blistering, tissue perforation, and hemorrhaging.[2] Capillary permeability also is increased as a result of vascular injury by lewisite, and the possible mechanisms for this effect include (1) direct action by lewisite on cell surfaces, (2) liberation of capillary-dilating substances from skin cells by lewisite, and/or (3) interference with the metabolism of capillary endothelial cells by lewisite.[5] Even though the precise mode of action of vesicants remains unknown,[22] it is the lipid solubility of lewisite that facilitates its penetration of tissue, including skin, and allows the compound to reach the capillaries and other cells that after injury produce blistering.[5,6] Furthermore, the associated edema and hemorrhaging can lead to shock and death.

Finally, in studies with laboratory animals, Cameron et al.[2] noted that ingestion of lewisite can produce acute inflammation of the mucous membrane of the stomach or intestine, which is characterized by hemorrhage, necrosis of epithelium, and submucous edema. The doses of lewisite producing such effects were never mentioned; however, this research also indicated that (1) the distribution of such lesions are determined by the mechanics of the alimentary tract, which are influenced by the presence or absence of food in the stomach at the time of ingestion, (2) occasionally, ingestion of a large dose of lewisite may lead to perforation of the stomach wall, and (3) systemic effects develop rapidly after ingestion, and the bile passages and liver cells are most severely affected. The injury to the bile passages and liver cells is probably related to presystemic extraction by the liver of any lewisite absorbed into the circulation from the gastrointestinal tract.

CARCINOGENICITY, MUTAGENICITY, AND TERATOGENICITY

Data about chronic toxicity resulting from the ingestion of lewisite have not been reported. In a review of the toxicity of arsenic and its compounds, Squibb and Fowler[27] suggest that the carcinogenic, mutagenic, and teratogenic properties of all arsenic species need more careful examination. For example, according to the literature cited in this review, arsenic may be (1) a cocarcinogen and act to promote the carcinogenic process; (2) capable of producing DNA damage, however, direct tests of mutagenicity

remain inconclusive; and (3) responsible for teratogenic effects, although organic arsenicals do not appear to cross the placenta or interfere with fetal development in mammals.

Recently, Hackett et al.[9] conducted a study to evaluate the maternal toxicity, intrauterine mortality, and developmental toxicity in rats and rabbits of lewisite following short-term multiple doses administered intragastrically. These intragastric doses of lewisite were administered once each day to pregnant animals on those days of gestation during which major organogenesis takes place. Accordingly, lewisite was administered to rats for 10 consecutive days (day 6 through 15 of gestation) and to rabbits for 14 consecutive days (day 6 through 19 of gestation). The results of this research were published in a 1987 report and suggest that maternal mortality is the primary factor in predicting the induction of maternal and fetal effects. Therefore, a no observed effect level for lewisite administered intragastrically to maternal animals should also represent a safe level for their fetuses. However, there were differences in the dose response relationships for lewisite between rats and rabbits, as exemplified by both the LD50 (median lethal dose) values for maternal animals (3.1 mg/kg for rats and 0.25 mg/kg for rabbits) and the no observed effect levels for maternal animals and their fetuses (between 1.5 and 2.0 mg/kg for rats and less than 0.07 mg/kg for rabbits). The authors indicate that such differences between dose response relationships for rats and rabbits might have occurred because the concentration of the lewisite in the solutions administered to the rabbits was about 13 times greater than that in the solutions administered to the rats. Another possibility is that the differences might be species related, i.e., maternal rabbits being more sensitive than maternal rats to lewisite toxicity, although this is not mentioned.

Because the aforementioned study examined the toxicity of lewisite in maternal animals following daily doses administered intragastrically for over 7 d, the data are useful for deriving the safe levels in water that can be recommended as interim short-term ($\leq$ 7-d exposure) field-water quality standards.

DEVELOPMENT OF ALTERNATIVE MAXIMUM PERMISSIBLE CONCENTRATIONS (MPCs) IN WATER

The available data concerning the health consequences of daily ingestion of lewisite comes from only three studies, all of which involve oral administration of lewisite to laboratory animals. The first of these studies is described in a 1941 report by Leitch et al.[8]

and involved the exposure of rats to lewisite-contaminated drinking water for a period of 133 d. The second study is presented in a 1987 report by Hackett et al.[9] and involved daily administration of lewisite intragastrically to both pregnant rats and pregnant rabbits for the 10 and 14 consecutive days of gestation, respectively, corresponding to organogenesis. As mentioned earlier the third and most recent study was performed by Sasser et al.[10] and was designed to evaluate the subchronic toxicity of lewisite administered by gavage to rats once each day, 5 d per week, for a period of 13 weeks. All three studies will be discussed, and the daily doses of lewisite that are reported in them to be no observed effect levels (NOELs) will be used to develop alternative maximum permissible concentrations (MPCs) in water for the compound and its trivalent-arsenic fraction (i.e., 36% by weight). The alternative MPCs will then be evaluated so that interim short-term ($\leq$ 7-d exposure) arsenic-based field-water-quality standards for lewisite for 5 and 15 L/d consumption rates by 70-kg military personnel can be recommended. Alternative MPCs were developed for evaluation because definitive dose-response data for ingestion of lewisite by humans could not be derived from the limited data presented in the three studies involving laboratory animals.

As part of the study by Leitch et al.,[8] 10 rats were administered drinking water containing a maximum concentration of lewisite of 16 mg/L for a period of 19 wk (133 d). The purpose of the study was to ascertain if field water contaminated with small amounts of lewisite (10 and 16 mg/L) could be consumed by military personnel under emergency conditions. Microscopic examination of the kidney, liver, spleen, stomach, and small intestine of the exposed populations of animals revealed no pathological changes that could be attributed to consumption of the contaminated water. Additionally, there appeared to be an absence of any pronounced effects on either growth or water consumption during the period of observation and any amount of variation in water consumption observed was attributed to evidence that environmental conditions in the animal room could have changed during the experiment (i.e., animals may have been exposed periodically to adverse conditions of excessive temperature, humidity, and drafts). Although one rat that was administered water containing lewisite at a concentration of 16 mg/L did die between the 60th and 70th day of the experiment and post-mortem changes in the animal were too advanced to determine the cause of death, two animals also died that were in the control group and another animal died that was in a group fed tap water containing a concentration of 7.63 mg/L of arsenious oxide (arsenic trioxide; As_2O_3). Arsenic trioxide was administered to the latter group of animals for the purpose of comparing the effects of equivalent doses of arsenic administered as either inorganic trivalent arsenic or lewisite. The control group consisted of 10 rats that were

fed tap water that was not contaminated with lewisite or arsenious oxide, and the principal cause of death for the two animals in this group appeared to be pulmonary disease. The cause of death for the animal that died in the group of 10 rats fed arsenious oxide could not be determined because post-mortem changes were too far advanced.

The reported absence of pathological changes in the organs, especially the stomach and small intestine, of the population of experimental rats fed water containing a lewisite concentration of 16 mg/L for a period of 133 d indicates that such a concentration of lewisite should not produce blistering in the tissues of any rats that consume the same amounts of lewisite per drink and per day as those in the experiment. However, the amount of water consumed by the rats per drink and the interval between drinks could not be determined from the data reported for the experiment. Such data are important for quantitatively estimating the maximum dose of lewisite that could be presented to the gastrointestinal tract, particularly the stomach and small intestine, at any given time that would not produce vesicant action or systemic toxicity.

Two other shortcomings of the study are its failure to define an effect level and to determine if the concentration of lewisite in the drinking water actually was 16 mg/L each day over the course of the experiment. For example, Leitch et al.[8] never determined the dose of lewisite that could produce blistering or systemic toxicity in the rats. Moreover, the lewisite concentration of 16 mg/L in the water fed to the rats should have been monitored over the course of the experiment because the stock solution of lewisite (containing a lewisite concentration of 128 mg/L; 529.4 mg of lewisite completely dissolved in 4136 mL of tap water) from which the contaminated water was prepared apparently was not made up freshly each day. Instead, it was diluted with tap water on an as-needed basis to obtain the drinking water for the rats. Consequently, if the lewisite in the stock solution decomposed over the extended period of time during which the experiment took place (i.e., 133 d), then the concentration of lewisite in the water fed to the rats may not always have been 16 mg/L. The experiments using fish reported by Price and von Limbach[26] suggest that lewisite and its hydrolysis products may undergo chemical changes in water over extended periods of time and that the resulting compounds will be less toxic than either lewisite or its hydrolysis products.

As a result of the two shortcomings just described, it is not possible to determine how near the 16 mg/L concentration of lewisite in water is to an effect level, particularly for vesicant action, and it must be assumed that the concentration of lewisite in the drinking water fed to the rats actually was 16 mg/L throughout the entire experiment. Consequently, if the 16 mg/L concentration of lewisite in water is substantially below the concentration that represents an effect level for rats, it is unlikely that any of the animals

in the experiment would have suffered any adverse effects. In fact, this would be true even if some of the animals ingested in a single drink, or in several drinks over a relatively short period of time, the maximum volume of water that could conceivably be presented to the stomach and small intestine of a rat at any time (i.e., the maximum possible dose of lewisite that could be delivered to these organs at any given time). However, if the 16 mg/L concentration of lewisite in water actually is near the effect level, then it is possible that none of the rats in the experiment exhibited any adverse effects such as irritation, blistering, or perforation of the stomach or small intestine because the experimental conditions prevented them from consuming enough water at any given time to deliver a toxic dose of lewisite to these organs.

Even though the data are limited from the rat study performed by Leitch et al.[8] because of shortcomings related to experimental design, the rats are considered to have been exposed to drinking water containing 16 mg/L of lewisite for at least 7 d. Furthermore, no adverse effects were attributed to the ingestion of this water by the rats even after 133 d. Therefore, a lewisite concentration in drinking water of 16 mg/L is believed to be a reasonable estimate of a NOEL value for at least short-term (≤7 d) ingestion of the compound in drinking water by rats. Accordingly, the estimated average daily dose of lewisite consumed by the rats in the experiment and considered to produce no adverse effects was approximately 1.4 mg/kg of body weight, which is equivalent to an average daily trivalent-arsenic dose of about 0.50 mg/kg of body weight. This daily dose of lewisite was calculated on the basis of the average amount of tap water that contained a concentration of lewisite of 16 mg/L (equivalent to an arsenic concentration of 5.8 mg/L) that was consumed daily by the animals (i.e., about 89 mL/kg per day; with a range of 79 to 107 mL/kg per day) and the average body weight of the animals over the course of the experiment (i.e., about 0.2 kg).

The teratology research using laboratory animals that was performed by Hackett et al.[9] also yielded dose-response data for lewisite from which MPCs may be developed. In these teratology experiments, lewisite was intragastrically administered each morning to pregnant rats and rabbits on the days of gestation corresponding to organogenesis (i.e., 10 consecutive days for the rat and 14 consecutive days for the rabbit). Not only were doses of lewisite administered to the maternal animals over a period exceeding 7 d, but also both maternal and fetal toxicity were looked for in all deceased animals and in the rats and rabbits sacrificed after 20 and 30 days of gestation, respectively. The results of these experiments indicated that maternal mortality was the most important predictor of the induction of maternal and fetal toxicity. Thus, the administered doses that correspond to the respective NOELs of lewisite for rats and

rabbits should not produce either toxic or teratogenic effects in these species, even if such doses were to be ingested daily in drinking water for a period lasting up to 7 d.

The effects of lewisite toxicity that were observed in maternal rats that received doses of the compound that proved to be lethal included an extremely flatulent gastrointestinal tract that was partially filled with yellow and bloody fluid and mucosal inflammation and hemorrhage. The typical lesions associated with lewisite toxicity in rabbits that received doses of the compound greater than the NOEL included inflammation, edema, and hemorrhage of the gastric mucosa. In fact, in those rabbits that died from lewisite toxicity, the mucosal inflammation and hemorrhage was more pronounced than in rats that died of lewisite toxicity.

Hackett et al.[9] also observed that dose levels inducing maternal mortality in rats differed remarkably from those inducing maternal mortality in rabbits. For example, the LD50 value for rats was calculated to be 3.1 mg/kg, but the LD50 value for rabbits was computed to be 0.26 mg/kg. An even larger difference exists between the daily dose of lewisite administered to rats for 10 consecutive days that was found to be a NOEL (i.e., 1.5 mg/kg), and the daily dose of lewisite administered to rabbits for 14 consecutive days that was determined to be a NOEL (i.e., less than 0.07 mg/kg). The researchers suggest that such large differences between LD50 values and NOELs for the two species might be attributed to the fact that the concentration of lewisite in the solutions administered to the rabbits was about 13 times greater than that administered to the rats. Such a conclusion is plausible because the immediate vesicant action of the compound on tissue, which is probably responsible for inflammation, edema, and hemorrhage, may be more a function of the concentration of lewisite in the solution in contact with the tissue than the equivalent dose of lewisite calculated for the whole animal. However, another explanation for the differences may be that the rabbit actually is the more sensitive species with respect to intragastrically administered lewisite. For example, the greater sensitivity of the rabbit might also be the reason why the researchers point out that even though gastric lesions were the most commonly observed injuries in animals of both species that died from lewisite toxicity, mucosal inflammation and hemorrhage was more pronounced in rabbits.

Regardless of whether or not the concentration of lewisite in a solution in contact with tissue may be important in determining the toxicity of a dose of the compound, or whether or not the susceptibility to lewisite toxicity following daily intragastric administration might be greater for rabbits, the results of probit analyses of the mortality data for both the rats and the rabbits that are presented by Hackett et al.[9] indicate that the response exhibited by the rat is greater for smaller increases in dose (i.e., the LD10 and

LD50 differ by a factor of only 1.5) than for the rabbit (i.e., the LD10 and LD50 differ by a factor of 4.5). However, this difference may be a function of how lewisite is administered. For example, Inns et al.[22] report that the LD50 for lewisite administered intravenously in a single dose to rabbits is 1.8 mg/kg and that the LD10 for lewisite administered to rabbits in exactly the same way is 1.5 mg/kg. The difference between the LD10 and the LD50 in this case is a factor of 1.2, which is similar to the difference between the LD10 and LD50 for rats that received a daily dose of lewisite intragastrically for 10 consecutive days. This implies that the slopes of the dose-response curves for rabbits intravenously administered lewisite in a single dose and for rats receiving a daily dose of lewisite intragastrically over 10 consecutive days may be the same. Unfortunately, the dose-response relationship for humans following ingestion of lewisite cannot be calibrated from any of these dose-response relationships for laboratory animals.

According to Hackett et al.,[9] the dose of lewisite administered each morning intragastrically to maternal rats for 10 consecutive days that corresponds to a NOEL is 1.5 mg/kg. The probit analyses of mortality data for lewisite administered each morning intragastrically to maternal rabbits for 14 consecutive days, which also was presented by Hackett et al.,[9] indicate that the lewisite NOEL for rabbits appears to be about 0.016 mg/kg.

As noted earlier, the third study that is of interest was performed by Sasser et al.[10] at Pacific Northwest Laboratory and is presented in an interim report dated March 1989. In this investigation, a dose of lewisite was administered to rats in a sesame-oil vehicle by intragastric intubation (gavage) once each day for 5 d per week over a period of 13 weeks (approximately 65 dosing days). The dose considered to be a NOEL appears to be between 0.5 and 1.0 mg/kg, because there was no observed adverse effects at the lower dose, but mild acute inflammation of the glandular stomach was observed in some cases at the higher dose. Accordingly, on the basis of the reported data for this study we consider the dose of 0.5 mg/kg to be the best approximation of the NOEL.

Table 2 summarizes the NOELs for lewisite that were obtained from the studies with rats by Leitch et al.[8]; the research with rats and rabbits by Hackett et al.[9]; and the experiments by Sasser et al.[10] involving rats. Interestingly, the daily doses equal to NOELs for rats obtained from the first two research efforts are in agreement. Also, the daily dose of lewisite equal to a NOEL for rabbits is between one and two orders of magnitude lower than that for rats.

The alternative MPCs in water for lewisite and its trivalent-arsenic fraction for consideration as recommended standards are developed from these NOELs based on a traditional approach to interspecies dose extrapolation. In this approach, the daily dose

Table 2. Summary of daily doses of lewisite and its trivalent-arsenic component representative of no observed effect levels (NOELs) for short-term ingestion by rats and rabbits.

Laboratory animal	Daily dose equal to NOEL (mg/[kg • d]) Lewisite	Arsenic fraction	Administration method	Period of exposure (d)	Ref.
Rat	1.4	0.50	In drinking water	133	8
Rat	1.5	0.54	Daily intragastric intubation in sesame oil	10	9
Rat	0.5	0.18	Daily intragastric intubation in sesame oil	~65	10
Rabbit	0.016	0.0058	Daily intragastric intubation in sesame oil	14	9

found to be a NOEL for a laboratory animal is divided by a safety factor; the objective of the safety factor being to protect humans against both acute and systemic effects and carcinogenic effects. Because of the shortcomings associated with the animal studies and the absence of information as to the suitability of either the rat or the rabbit as an appropriate animal model for humans, safety factors of 1, 10, and 100 are used and the resulting MPCs are all evaluated for their applicability as standards. A safety factor of unity implies that there are no uncertainties associated with interspecies differences between a particular laboratory animal and humans. The more a safety factor exceeds unity, the greater the uncertainties associated with interspecies differences between a particular laboratory animal and humans. A value of 100 is the maximum safety factor used based on recommended guidelines for extrapolating dose-response data available from long-term feeding studies with animals.[28,29] After the dose to the animal has been divided by a safety factor, an MPC is calculated by multiplying that result by the standard weight assumed appropriate for military personnel (i.e., 70 kg) and then dividing the product by a consumption rate (e.g., 5 or 15 L/d for military personnel). The alternative MPCs for lewisite and its arsenic fraction in water that were developed by this method from the NOELs for rats and rabbits are presented in Table 3 for evaluation.

Table 3. Maximum permissible concentrations (MPCs) in water for lewisite and its trivalent-arsenic component for consideration as possible field-water-quality standards for 5 and 15 L/d consumption rates by 70-kg military personnel for a period lasting up to 7 d determined from three alternative safety factors. Developed from daily doses representative of no observed effect levels (NOELs) for short-term ingestion by rats and rabbits.

			MPCs for consideration as field-water-quality standards (mg/L)											
	Ingested daily dose equal to NOEL (mg/kg•d))		Safety factor of 1				Safety factor of 10				Safety factor of 100			
			Lewisite		Arsenic-fraction		Lewisite		Arsenic-fraction		Lewisite		Arsenic-fraction	
			Consumption rate (L/d)		Consumption rate (L/d)		Consumption rate (L/d)		Consumption rate (L/d)		Consumption rate (L/d)		Consumption rate (L/d)	
Laboratory animal	Lewisite	Arsenic fraction	5	15	5	15	5	15	5	15	5	15	5	15
Rat	1.4[b]	0.50	20	6.5	7.1	2.4	2.0	0.65	0.71	0.24	0.20	0.065	0.071	0.024
Rat	1.5[b]	0.54	21	7.0	7.6	2.5	2.1	0.70	0.76	0.25	0.21	0.070	0.076	0.025
Rat	0.5[c]	0.18	7	2.5	2.5	0.91	0.7	0.25	0.25	0.091	0.07	0.025	0.025	0.00091
Rabbit	0.016[d]	0.0058	0.22	0.075	0.08	0.027	0.022	0.0075	0.008	0.0027	0.0022	0.00075	0.0008	0.00027

[a]A safety factor of unity implies that there are no uncertainties associated with interspecies differences between a particular laboratory animal and humans. The more a safety factor exceeds unity, the greater the uncertainties associated with interspecies differences between a particular laboratory animal and humans. A value of 100 is used for the maximum safety factor based on recommended guidelines for extrapolating dose-response data available from long-term feeding studies with animals.[28,29] Generally, safety factors are applied to animal data so that resulting doses will protect humans from health effects that include both acute-systemic effects and carcinogenic effects.

[b]From data reported in Ref. 8 (see Table 2).

[c]From data reported in Ref. 10 (see Table 2).

[d]From data reported in Ref. 9 (see Table 2).

EVALUATION OF ALTERNATIVE MPCs AND RECOMMENDATIONS FOR INTERIM SHORT-TERM ARSENIC-BASED FIELD-WATER-QUALITY STANDARDS FOR LEWISITE

The alternative MPCs presented in Table 3 can be evaluated only qualitatively and judgmentally for consideration as possible field-water-quality standards. A quantitative analysis is not possible because the alternative MPCs for consideration as possible field-water-quality standards could only be developed for military personnel by applying a safety factor of either 1, 10, or 100 to daily doses considered NOELs for ingestion that were derived from limited research involving two species of laboratory animals. Therefore, until more definitive data concerning the response of humans to ingested lewisite become available, the field-water-quality standards that are recommended should be considered interim ones. Furthermore, the field-water-quality standards for lewisite that are recommended will be based on the trivalent-arsenic fraction of the compound for the following reasons. First, lewisite would presumably contaminate field water initially, but the lewisite would then undergo rapid hydrolysis to lewisite oxide. Second, the rapid vesicant action and toxicity of lewisite or lewisite oxide is attributed to the relatively rapid lipid solubility of the trivalent-arsenic that is part of these compounds. Finally, the test for lewisite in field water that is used by the U.S. military is based on detecting its arsenic component and not the parent compound or the oxide.

Among the alternative arsenic-based MPCs for lewisite presented in Table 3, those based on rabbit data and a safety factor of unity are the ones recommended as interim field-water-quality standards (i.e., 0.22 and 0.075 mg/L for lewisite for 5 and 15 L/d consumption rates, respectively; and 0.08 and 0.027 mg/L for arsenic for 5 and 15 L/d consumption rates, respectively). This recommendation is made for the following reasons.

First, Inns et al.[22] compared the toxicity of sodium arsenite and lewisite following intravenous administration to rabbits and found that on the basis of trivalent-arsenic content lewisite was 6.5 times more toxic than sodium arsenite. This suggests that arsenic-based MPCs for lewisite should be between a value that is equal to and a value that is 6.5 times lower than the field-water-quality standards recommended as short-term standards for field water for total inorganic arsenic (a portion of which is considered to be trivalent arsenic) in Chapter 7 of Part 1 of this volume (i.e., 0.3 and 0.1 mg/L for 5 and 15 L/d consumption rates, respectively).[15] Accordingly, the recommended arsenic-based MPCs for consideration as field-water-quality standards for lewisite meet this requirement because they are almost four times lower than the

recommended standards for total inorganic arsenic. Those MPCs based on the NOELs from all experiments using rats[8-10] and application of a safety factor of unity do not meet this criteria and so are excluded from further consideration. Similarly, MPCs in Table 3 based on NOELs from the experiments with rats reported by Leitch et al.[8] and by Hackett et al.[9] that are divided by a safety factor of 10 also are not considered for recommendation because these MPCs also do not meet the necessary criteria. Furthermore, even though the rat NOEL from the most recent animal study[10] divided by a safety factor of 10 does lead to MPCs that barely meet the essential criteria, these MPCs are not used. The reason these MPCs are also excluded from further consideration is that they exceed concentrations of lewisite (or its arsenic equivalent) in water that are derived on the basis of dividing the lowest dose reported by Hackett et al.[9] to produce mortality in rabbits (0.07 mg/kg) by a safety factor of 10. The decision to use a safety factor of 10 in this case is completely judgmental, and naturally the corresponding concentrations must be considered very conservative. Nevertheless, for purposes of this comparison and because of the severity of the outcome (i.e., death) the use of a safety factor of 10 for extrapolating this dose from rabbits to humans is considered appropriate.

Second, the rabbit may be the most sensitive animal species, and might even be more sensitive than humans with respect to intragastrically administered lewisite. Indeed, the available experimental data shown in Tables 2 and 3 indicate that the daily dose of lewisite equal to a NOEL for the rabbit is at least 30 times less than the NOEL for rats (based on the most recent study involving rats, see Ref. 10) and may be as much as 100 times lower (based on earlier work with rats, see Refs. 8 and 9). Thus, there is some amount of conservatism built into using this rabbit NOEL without a safety factor (i.e., a safety factor of unity) as the basis for recommending field-water-quality standards for lewisite. Furthermore, the rabbit NOEL is approximately the same order of magnitude as all of the rat NOELs after division by a safety factor of 100. Additionally, use of the rabbit NOEL without application of a safety factor is considered valid for another reason. Safety factors are normally applied to ensure protection against both acute-systemic health effects and carcinogenesis, given the uncertainties associated with interspecies extrapolation. However, the potential risk of cancer is not considered a relevant factor in the context of establishing military field-water-quality standards for short-term ($\leq$ 7-d) exposure to field water containing threat agents such as lewisite. Thus, an even more conservative estimate of the NOEL is not considered necessary.

Finally, even though the MPCs for lewisite that are derived on the basis of dividing the NOELs from the study involving rabbits[9] by a safety factor of 100 should be more than adequate to protect military personnel from performance-degrading health effects, such

MPCs are not recommended as interim standards. This is because these levels of lewisite are so low as to be inconsequential, particularly with respect to concentrations of other arsenic species that may be present in field water.

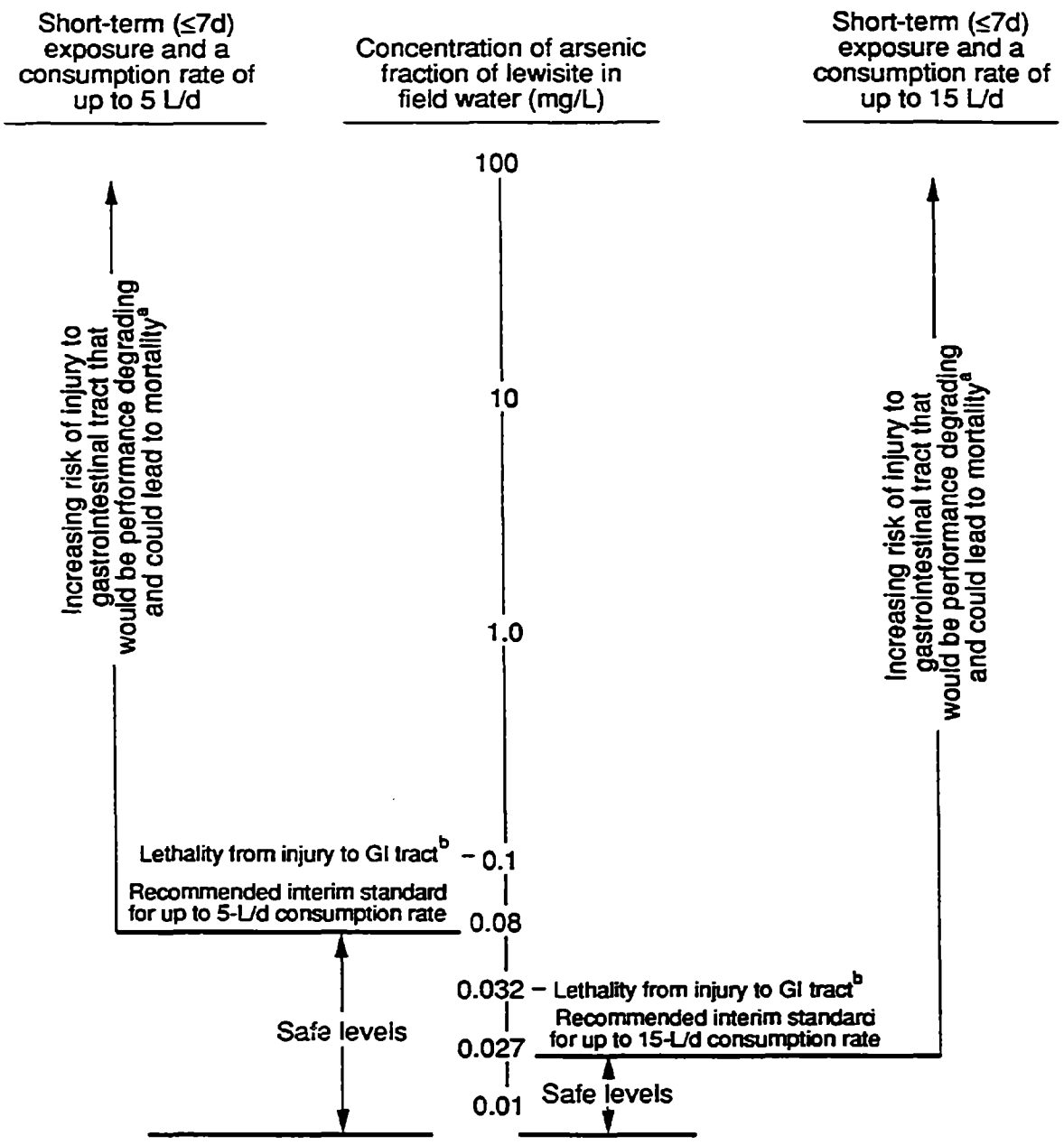
In conclusion, it is apparent that the arsenic-based MPCs for lewisite that are recommended as interim standards are going to require improved monitoring techniques for detection. Nevertheless, on the basis of the available animal data they are not so low as to be inconsequential in field water.

RISK ASSESSMENT

Figure 1 is a visual guide for assessing the impact of arsenic-based concentrations of lewisite that exceed the recommended interim standard. The figure shows that arsenic-based concentrations of lewisite in field water above levels recommended as interim standards can lead to performance-degrading health effects produced by injury to the gastrointestinal tract that, according to evidence from animal experiments, may even be lethal. Data from animal studies also indicate that this injury could include pronounced hemorrhage and inflammation of the mucosa, as well as gastric edema.[9]

SUMMARY AND CONCLUSIONS

The recommended arsenic-based interim field-water-quality standards for lewisite for short-term exposure (≤ 7 d) by military personnel are 0.08 and 0.027 mg/L for 5 and 15 L/d consumption rates. These recommendations for interim standards were developed by applying a safety factor of unity to the daily dose of the arsenic fraction of lewisite considered to be a NOEL for ingestion by rabbits for a period lasting up to 7 d. Interim standards based on an even more conservative estimate of the NOEL (i.e., incorporation of a safety factor greater than unity into the calculation) are considered inappropriate because rabbits appear to be the most sensitive to the acute-systemic effects of lewisite and because potential risk of cancer is not considered a relevant factor in the context of establishing military field-water-quality standards for short-term (≤ 7-d) exposure to field water containing threat agents such as lewisite.



[a] Based on extrapolation from effect of doses above NOEL for rabbits.[9]

[b] Based on lowest dose reported to produce mortality in rabbits.[9] [0.07 mg/kg x 0.1 safety factor x 70 kg/5 or 15 L/d]

Figure 1. Health-effects summary for lewisite (based on the NOEL for the rabbit; the most sensitive species).

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CHAPTER 7. RESEARCH RECOMMENDATIONS

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INTRODUCTION

Research that will help reduce important sources of uncertainty or strengthen confidence in the recommended standards for the OP nerve agents, mycotoxin T-2, and lewisite are identified in this chapter. Such research recommendations for cyanide are discussed in detail in the first part of this volume and are applicable to hydrogen cyanide. These recommendations include measuring the magnitude of (1) the fraction of ingested cyanide that is available for systemic circulation after first-pass detoxification in the liver and (2) the amount of unmetabolized cyanide that can be excreted in sweat because these processes may be significant for detoxifying and eliminating cyanide. There is sufficient confidence in the standards recommended for radioactivity on the basis of the available data that additional research is not recommended.

RECOMMENDATIONS FOR PROTOCOLS FOR ASSESSING HUMAN HEALTH EFFECTS ASSOCIATED WITH THE CONSUMPTION OF MILITARY FIELD WATER CONTAMINATED BY THREAT AGENTS

The threat agents of interest to military personnel from the perspective of field-water contamination in a chemical warfare (CW) environment include (1) the organophosphorus agents VX, GD, GB, and GA, (2) T-2 mycotoxin, and (3) lewisite, an arsenical vesicant. The recommended field-water-quality standards for these compounds for consumption rates up to 5 and 15 L/d over an exposure period lasting up to 7 d are deemed interim ones because the data needed to derive them come from a small number of experiments with laboratory animals and a few studies involving human volunteers. To compensate for the absence of definitive data, these field-water-quality standards were developed using conservative assumptions. Therefore, in this chapter, we generally describe the experimental protocols that are needed to validate the interim

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recommendations or to revise them so they more accurately reflect safe levels, and to verify or better determine the possible health effects that would impair military performance if recommended levels are exceeded.

The protocols we recommend involve the testing of specific laboratory animals for evidence of toxicity. We propose that the respective compounds be administered orally in repetitive doses to the animals at various concentrations in water (or an appropriate vehicle) over an exposure period of 7 d. Dose-response data from such studies can then be extrapolated to military personnel for drinking-water consumption rates up to 5 or 15 L/d over the same exposure period. These results should be compared to the recommended interim standards so that such interim standards can be verified or revised accordingly. The acute health effects, especially the neurotoxic and behavioral effects, that can result from short-term exposure to repetitive oral doses of threat agents are of primary concern. Additionally, the protocols can be adapted to determine if field-water-quality standards should be considered for the environmental degradation products of the threat agents of concern.

The assumptions for devising the protocols and the criteria for selecting appropriate animal models are described first. Separate discussions concerning each of the threat agents of military concern include a general description of the recommended test protocol for each compound.

ASSUMPTIONS FOR PROTOCOLS AND CRITERIA FOR SELECTING ANIMAL MODELS

Toxicity testing requires extreme care in experimental design, test species selection, dosage regimen for the test agent, clinical observation, selection of appropriate physiologic or behavioral tests for assessing health effects, data collection, statistical analyses, and interpretation. Despite attention to all of the above, it is difficult, if not impossible, to design test protocols that will be identical to the conditions of human exposure to the substances in question.

For the determination of the safety of the proposed water quality standards for the various threat agents, several assumptions have been made:

- at agents for which interim field-water-quality standards have been recommended are OP threat agents, T-2 mycotoxin, and lewisite.
- The population at risk will consist of predominantly healthy males 18 to 55 years old. If the population at risk includes both males and females, then the testing should include both sexes.

- The maximum exposure period for the soldier will be 7 d with total dose of threat agent dependent upon the ingestion of either 5 or 15 L/d of water. Longer periods of exposure are not considered.
- Oral administration represents the type of exposure corresponding to consumption of field water by military personnel. The route of exposure for the threat agents to the test animals should be by oral ingestion of contaminated water using gavage to insure complete administration.
- To determine the amount of threat agent that individuals might be exposed to on a mg/kg basis, the average adult weight of 70 kg will be used.
- The effect(s) of the threat agents on organ systems, particularly the nervous system, that would cause performance degradation are of primary interest. Although mutagenicity, carcinogenicity, and teratogenicity are important considerations in toxicity testing, they are not of prime importance in the proposed testing protocols.
- Food sources will be free from significant contamination with the particular threat agents in question.
- Test protocols do not take into consideration exposure to a combination of threat agents.
- While the cost of conducting toxicity tests was an important consideration, it was not a major factor in our recommendations.

To minimize the potential for error in interpreting test results, several conservative approaches to toxicity testing are recommended:

- The most toxic forms of threat agents should be used. For example, even though VX is considered to be the most acutely toxic organophosphorus (OP) threat agent based on administration of a single oral dose, GD (soman) may be even more toxic than VX based on repetitive subacute doses. Thus, all OP compounds should probably be examined to be sure the most toxic one for repetitive subacute doses is identified. Additionally, the degradation products of threat agents may possess toxic properties as well. Therefore, the testing protocols are generally applicable for addressing those toxic compounds that might result following environmental degradation of parent threat-agent compounds.
- Testing should include untreated controls, vehicle-treated controls (if appropriate), and positive controls (toxic levels of the threat agent).
- Doses of threat agent should be administered to test animals according to two dosage schemes, both all at once and in divided doses over time, so that differences in toxicity depending on dosing regimen can be determined.

- A sensitive species of test animal should be used. If possible, the LD50 in the recommended test animal species should be similar to the known lethal dose for man. If human data are not available, then the most sensitive animal species should be selected for use.
- More than one species should be tested (normally a minimum of one rodent species and one nonrodent species).

The recent trend in toxicology has been toward the development of in vitro tests that would be predictive of in vivo toxicity. We considered in vitro tests for the proposed protocols and recommend them where appropriate; however, more useful information would be gained with live-animal testing in most of the protocols because of the emphasis on human performance degradation.

We recommend that the testing be done using Good Laboratory Procedures including these specific recommendations:

- Personnel must be appropriately educated, trained, and experienced for the tests being conducted.
- Board certification is recommended for those individuals responsible for the comparative pathology and toxicity testing.
- Test substances should be analyzed for purity and uniformity throughout the study.
- Test substances should be administered daily by oral gavage at the same times of day, for seven consecutive days.

Perhaps the most critical phase of the experimental design is the species selection. Therefore, it is important to consider the criteria used for selecting animal models for determining human health problems. A partial list of such criteria would include: precedent, animal costs, physiologic similarity to man, size, appropriate lifespan, proven procedures, availability, data base, and ethics. Obviously, no single animal model can be the "best" human model for all these criteria. Normally the investigator will make the selection based on several of these criteria. Therefore, every animal model is a compromise.

The threat agents are known to be toxic substances; therefore, we believe a narrow dose range is appropriate. Daily doses should begin at the recommended interim standard and gradually increase.

The extrapolation of laboratory animal data to humans has been successful when three conditions are met: (1) data are available from several species, (2) the toxic mechanisms (biochemical lesions) of the test substance are known, and (3) other similar compounds have been successfully extrapolated to humans from the same animal species.

Problems with extrapolations from laboratory animals to man may occur when the species differences are great, inappropriate dose levels are used, poor experimental designs (especially lack of untreated or positive controls) are employed, and routes of administration are different.

We believe that the tests recommended herein can be done mainly in two species: the laboratory albino rat (Rattus norvegicus) and the Rhesus monkey (Macaca mulatta). These species have been used previously for similar testing, and they represent acceptable compromises as demonstrated with regard to metabolism of 65 different xenobiotic substances.[1]

The laboratory rat can be used in large numbers to provide statistical significance and, in most cases, previous data exist regarding the substance in question in rats. The Rhesus monkey is being recommended based upon the interest in the neurobehavioral toxicology of the test substances. Nonhuman primates, such as the Rhesus monkey, provide the best phylogenetic similarity to humans and are capable of a wide range of neurobehavioral testing paradigms. In some cases, other species are suggested where appropriate (e.g., laying hens for organophosphorus-induced delayed neuropathy (OPIDN) testing).

The animals should be of uniform weight, age, and strain. The animals must be handled, fed, and housed in a manner consistent with the requirements outlined by the National Institutes of Health (NIH) in Guide for the Care and Use of Laboratory Animals.[2]

According to the U.S. Environmental Protection Agency (EPA),[3] "acute oral toxicity" is defined as any adverse effect which occurs as a result of the oral administration of a single dose of a test substance. A "subchronic" study would involve test substance administration over a period of not less than 90 d. We recommend a dose regimen of daily oral administration of the test substance for 7 d to conform with exposure of military personnel. Therefore, our recommended protocols are technically neither acute nor subchronic tests. Instead, the protocols are a modification of normal acute testing. Such protocols should follow the recommendations of EPA for acute oral toxicity testing of pesticides to humans and domestic animals.[3]

RECOMMENDED PROTOCOLS FOR THE THREAT AGENTS OF MILITARY CONCERN

This section is divided into separate discussions for each of the threat agents of military concern. Each discussion identifies the experimental protocols that would be useful for validating or revising recommended interim standards and verifying or better

determining the possible health effect that could result if recommended standards are exceeded.

ORGANOPHOSPHORUS THREAT AGENTS

Exposure to toxic levels of OP threat agents would result in incapacitation of exposed personnel. Exposure to nonlethal yet toxic levels may also result in varying degrees of performance degradation dependent on the level of exposure. Neurological effects have been demonstrated to occur in humans exposed to subclinical levels of OPs.[4] Common symptoms of OP poisoning such as nausea, vomiting, and diarrhea could significantly impact performance ability. Delayed effects such as OPIDN or chronic alterations in EEG activity may have more subtle yet significant effects on performance.

Cholinesterase (ChE) assays are the only widely used method for determining an exposure to an OP threat agent, and therefore, the computation of a human field-water-quality standard must be based upon any data on ChE inhibition by OP threat agents available in the literature. Unfortunately, there is not a clear relationship between levels of ChE inhibition and definite neurobehavioral effects. This represents an area of research that is currently being investigated using alternative methods for determining the significance of ChE inhibition.

Consequently, suggested protocols include monitoring ChE activity along with behavioral changes, clinical signs, and pathologic lesions in laboratory animals. The protocols will determine whether or not there are biological effects more suitable than ChE inhibition in rats for determining the potential for performance-degrading health effects in military personnel following ingestion of OP threat agents in field water over time. If such biologic effects are documented, then the interim field drinking-water standards might need to be revised. Additionally, all OP threat agents shall be tested by the protocols so that the relative toxicity of each one can be determined with respect to ingestion in divided doses over the course of 7 d. Similarly, the protocols can be used to examine the toxicity of the products of degradation of the OP threat agents in the environment.

Assessment of mental and behavioral effects is essential when studying the toxicity of the ChE inhibiting OPs. Due to the extreme toxicity of the OP threat agents, manifestations may occur even at low exposure levels. Along with the potential for acute effects, the potential for chronic or delayed effects exists. Therefore, we recommend that in addition to general toxicity testing, OP-treated animals should be further evaluated for behavioral changes and the onset of delayed neuropathies.

The following biological markers should be included in all assessments of OP toxicity:

- Daily erythrocyte and plasma ChE measures.
- Standard clinical EEG and EEG spectral analysis.

New benchmarks for determining the thresholds for toxic effects should also be found that correlate better with the recovery from toxic effects than do blood cholinesterases. Furthermore, the role of detoxifying enzymes and aging of cholinesterase in the toxicity of OP threat agents ingested in divided doses over time needs to be better described.

We suggest the use of the rat and the Rhesus monkey for the toxicity assessment of the OP nerve agents. The rat is an appropriate test animal for OP toxicity due to the wealth of background information on it, its susceptibility to effects, and its ability to perform in behavioral tests. The Rhesus monkey was chosen for its physiological similarity to humans and its ability to perform complex behavioral tests. The Rhesus monkey can also tolerate the daily clinical procedures, such as blood samples, necessary for adequate monitoring of toxic effects. Also, OPIDN should be evaluated further in studies with laying hens and also rodents. Appendix A describes a protocol suitable for assessing decrements in behavior associated with exposure to OP agents.

THE TRICHOTHECENE MYCOTOXIN T-2

Acute toxicity studies of T-2 and clinical trials of diacetoxyscirpenol (DAS, another trichothecene mycotoxin with chemical and toxicological similarity to T-2 toxin) in experimental animals to determine its effectiveness in humans as a chemotherapeutic agent for treating cancer show that exposure to a sufficient amount of T-2 toxin would result in rapid performance degradation. The onset of nausea and vomiting can occur within a matter of minutes with vomiting persisting for several hours. If supportive therapy is not initiated quickly, the onset of circulatory shock could be rapid. However, the performance-degrading effects of T-2 toxin on the CNS have not been thoroughly evaluated.

Alterations in clotting mechanisms or suppression of the immunocompetence of exposed individuals, which also are possible effects of exposure to T-2 toxin, could adversely impact on the ability to perform normal duties. Therefore, the effect of T-2 toxin on the hematopoietic and immune systems also need careful examination.

The trichothecene mycotoxin, T-2, is not readily water soluble. However, it is soluble in ethanol, and a relatively dilute solution of ethanol and normal saline (50:50 or less ethanol) would be an appropriate vehicle for the administration of T-2 toxin by oral gavage.

The experimental animals recommended for use in validating or revising the field-water-quality standards for T-2 toxin would be the rat and the nonhuman primate (Rhesus monkey) or swine. The nonhuman primate is suggested in order to evaluate any behavioral effects that may occur. If the use of nonhuman primates is not possible, swine would be the second choice. While the ability to evaluate behavioral abnormalities would be more difficult in swine, they would be a good model for the evaluation of possible cardiovascular effects of T-2 toxin. There is a substantial amount of information on the effects of T-2 toxin in all three species, but much of these data are for single doses of T-2 toxin administered by routes other than the oral one.

In addition to a general toxicity-testing protocol, additional testing should focus on the hematopoietic, immune, and nervous systems. Appendix A describes a protocol suitable for assessing decrements in behavior associated with exposure to T-2 toxin.

LEWISITE

Lewisite is an arsenical compound that, in addition to the ability to cause acute arsenic toxicosis, has a vesicant action. This vesicant action appears to be related to the concentration of lewisite in immediate contact with tissue and, following ingestion, could be expected to lead to incapacitation prior to the onset of any arsenic toxicosis. However, on the basis of data currently available in the literature, this relationship between vesicant action and arsenic toxicosis can only be assumed. In fact, data from studies involving the ingestion of lewisite by laboratory rabbits and rats over time are the only data suitable for developing recommendations for interim standards and are only used for helping to estimate no observed effect levels (NOELs) for lewisite in field water. Also, the rat may not be an appropriate animal model for correlating lewisite toxicity to humans because, unlike humans, the rat apparently does not eliminate arsenic rapidly from the blood[5,6] and this may be relevant from the standpoint of lewisite toxicity in humans.

For the reasons just mentioned, protocols should be employed that use animal models known to have metabolic and anatomical similarities to humans. Furthermore, the protocols should determine if there are doses of lewisite at which vesicant action does produce performance-degrading health effects that are detectable physiologically or behaviorally prior to the manifestation of any such effects as a result of arsenic toxicity.

Due to its physiological similarity to man, the Rhesus monkey is recommended as a good animal model to use in such protocols, and lewisite should be administered in divided doses over the course of a day. A behavioral testing protocol that might be used is described in Appendix A.

SUMMARY

The recommended protocols for research are purposely broad to allow the user to apply them to other related threat agents with minimal changes. This type of verification testing with positive controls (toxic levels of each agent) will be useful in validating or revising standards and for the computation of health risks.

APPENDIX A
NEUROBEHAVIORAL ASSESSMENT PROTOCOL

Given the complexity of the interactions of the nervous system with other organs in the body, it is logical to assume that changes in nervous system function may occur at doses of a toxicant lower than those required to produce morphologic or other changes.[7] As a result, neurobehavioral measures are being increasingly relied upon to study and assess toxic effects of environmental pollutants. These behavioral measures are used to provide toxicologic information that may not be provided by conventional tests of pathology or lethality. For this protocol, neurobehavioral assessments will include one or more tests from each general neurobehavioral category (i.e., sensory, motor, or cognitive).

Techniques employed to study neurobehavioral parameters range in complexity from simple observations (e.g., cage-side observations[8]) to in-depth resource-intensive procedures (e.g., computerized sensory-evoked potentials[9]). Selection of specific tests to use in neurobehavioral assessment is dependent upon species, number of animals per treatment group, toxicant of interest, time course of effects, and the similarity in physiologic response to man.

This neurobehavioral test battery should include testing procedures that do not require highly trained test animals and can accommodate large numbers of animals. The tests can be conducted on the same animals repeatedly. Cognitive tests require more training, but these tests will be necessary for validating the safety of the interim field-water-quality standards. In the next section, we describe the specific behavioral testing to be done in the rodent species for the appropriate threat agents. Next, we present the neurophysiologic testing that we recommend be done in both rodents and nonhuman primates for direct comparisons of the species. These electrophysiologic techniques can also be done in cases of actual human exposures. Finally, we discuss the detailed cognitive testing to be done in nonhuman primates (not rodents) that can be used for modeling the human performance decrements or cognitive alterations. We also mention the limited amount of general cognitive testing that can be done in the rodents.

BEHAVIORAL TESTING—RODENTS

Primary measures for rodents will include one or more procedures to assess each of the three general neurobehavioral categories previously mentioned.

Sensory

Startle response may be used for a thorough assessment of sensory functions (auditory, visual. and tactile stimuli). Startle response quantifies the response of the animal to a specific sensory stimulation (e.g., the body flex of the animal in response to a puff of air on its whiskers). Davis[10] provided a comprehensive review of drug effects on startle responses.

Motor

Primary testing for behavioral toxicity in this functional category can be done using Forelimb Grip Strength[11] to measure muscular weakness and Activity Monitoring to analyze spontaneous activity. The Figure-8 Residential Maze with ambulatory and rearing information has been successfully used for activity monitoring following environmental neurotoxic exposures.[12] The Figure 8 represents a continuous "burrow" for quantifying the normal exploratory behavior of the ground dwelling mammal. Normally one will monitor the movements of the animal overnight. An Accelerating Rotarod procedure may be used to further assess motor function and coordination.[13] The rotarod requires the rodent to balance on a motorized rod. The rod is slowly accelerated and the time the animal stays on the rod is the primary indicator of performance.

Cognitive

Primary testing for neurobehavioral toxicity in this functional category can be done using such methods as the Potentiated Startle Response with classical conditioning.[14] In this test, the startle responses of the rodents are elicited as usual by a stimulus following a training session (10 trials) where mild electrical shock is paired to the stimulus. After the short training period, the response times of the rodents will be shorter and more intense. Therefore. you are modifying the normal response by a previously conditioned stimulus and measuring the ability of the animal to remember the association between the stimulus and the paired shock.

NEUROPHYSIOLOGIC TESTING—RODENTS AND PRIMATES

In the previous section, we presented general neurobehavioral toxicity testing of behavioral function. Neurophysiologic assessment can be used to measure changes in

specific CNS functions as reflected by electrical activity of the brain. Sensory-evoked potentials (SEPs) are an example of a neurobehavioral technique that has become increasingly popular as both a research tool and as a clinical diagnostic aid for evaluating general neural function. The SEPs are useful for determining CNS function because they are time-locked to specific stimuli.[15] The use of a variety of controlled external stimuli (e.g., light or sound) allows information to be obtained regarding the integrity of CNS receptors and neuroanatomical pathways.[16-18] The results obtained from these types of recordings are representative of neural activity in the area of the recording electrodes. Alterations in amplitude and latency of the sensory evoked response will be influenced by compounds affecting the CNS. These changes in brain responses to various stimuli are indicators of changes in behavior (at the neural electrical level). One assumes that changes in SEPs by the threat agents would represent an increased probability that the performance of military personnel may also be affected. An advantage of using SEPs lies in the fact that similar tests may be performed in human and nonhuman (e.g., rodents and monkeys) test species.[19]

Because the SEPs are specific for the particular stimulus used, it allows the user to separate the various components of the CNS rather than making generalized statements of gross decrements in CNS function as determined by standard behavioral experiments. The primary CNS pathways evaluated using the SEP methods are the visual, auditory, and somatosensory.

The visual evoked potentials are divided into flash evoked potentials (FEPs) and pattern reversal evoked potentials (PREPs). Of these two types of SEPs, pattern reversal is most commonly used in assessing brain dysfunction in humans while the flash evoked potential is commonly employed in nonhuman vertebrate (e.g., rat) studies.

The brainstem auditory evoked potential (BAEP) is a measure of the electrical activity generated by the subcortical components of the auditory system at levels from the eighth cranial nerve to the inferior colliculus. This SEP has been shown to be an extremely sensitive measure of sensory neural processing, as seen in the guinea pig treated with GD, and can index subtle neural damage not readily detectable using traditional methods,[20] thus illustrating the importance of using SEPs for validating the safety of the threat agents.

Somatosensory evoked potentials (SSEPs) allow for assessment of the integrity of peripheral sensory nerves. These responses are recorded from the skull following stimulation of a peripheral nerve and consist of both distal (i.e., near the stimulus) and local (i.e., near the recording electrodes) components.[19,21] The response obtained is dependent not only on the intensity of the stimulus used but also on the location of the

nerve stimulated.[19,22-23] Because of the degree of variability between test subjects, the appropriate intensity of the stimulus should be determined for each subject.

COGNITIVE TESTING--PRIMATES

In-depth assessment of cognitive function should be done with primate test animals. A cognitive conditioned response model such as the Delayed Match-to-Sample (DMS) test is recommended. This task requires the monkey to remember a previously presented color stimulus and to properly identify the stimulus in later trials to receive a banana-flavored food pellet. This type of behavioral assessment with Rhesus monkeys has been reported.[24]

Assessment of complex task performance ability may be done using a combination of the Primate Equilibrium Platform (PEP), and Multiple Alternative Response Task (MART). Use of the PEP and MART tests for assessing complex performance ability in adult male Rhesus monkeys after exposure to anticholinergics, anticholinesterases, and ionizing radiation have been reported, (e.g., benactizine by Farrer et al.[25]). This type of testing allows for a more direct comparison of the performance of the monkey to that of an aircraft pilot.

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DISCLAIMER

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