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Evaluation of Military Field-Water Quality

Volume 4. Health Criteria and Recommendations for Standards

Part 1. Chemicals and Properties of Military Concern Associated with Natural and Anthropogenic Sources

Jeffrey I. Daniels (Editor)

February 1988

Lawrence Livermore National Laboratory

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The purpose of this report is to develop drinking water standards for field-water constituents and properties of military concern that are naturally occurring or anthropogenically introduced under peacetime conditions. 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 field-water. Standards are recommended that address both short-term (up to 7 d) and long-term (up to 1 y) field-water consumption at rates of 5 and 15 L/d. Turbidity and color are the physical properties of concern because they can adversely impact the organoleptic quality (e.g., taste, odor, or appearance) of field water and thereby lead to reduced water consumption and subsequent involuntary dehydration, which can degrade performance. Total dissolved solids, chloride, magnesium, sulfate, inorganic arsenic, cyanide, the pesticide lindane, and metabolites of aquatic algae and associated bacteria (i.e., geosmin

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and methylisoborneol) are the chemical constituents of concern because they can be responsible for degrading performance directly as a consequence of their toxic properties and/or indirectly by adversely affecting the organoleptic quality of field water, which can result in reduced water consumption and an increased risk of dehydration.

This report is part one 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 2), Health Criteria and Recommendations for Standards: Interim Standards for Selected Threat Agents and Risks from Exceeding These Standards; 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; Vol. 9, Data for Assessing Health Risks in Potential Theaters of Operation for U.S. Military Forces.

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Project Officer: S. A. Schaub

L. R. Anspaugh, J. I. Daniels, and D. W. Layton
Principal Investigators at Lawrence Livermore National Laboratory

FOREWORD

This report is part one 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 2), Health Criteria and Recommendations for Standards: Interim Standards for Selected Threat Agents and Risks from Exceeding These Standards; 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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The principal investigators at the Lawrence Livermore National Laboratory (LLNL), Drs. Jeffrey Daniels, David Layton, and Lynn Anspaugh, extend their gratitude and appreciation to all of the participants in this study for their cooperation, assistance, contributions and patience; especially to Dr. Stephen A. Schaub, the project officer for this monumental research effort, and to his military and civilian colleagues and staff at the U.S. Army Biomedical Research and Development Laboratory (USABRDL). A special thank you is extended to the editors, secretaries, and administrative personnel of the Environmental Sciences Division at LLNL, particularly to Ms. Barbara Fox, Ms. Yvonne Ricker, Ms. Penny Webster-Scholten, Mr. E.G. Snyder, Ms. Gretchen Gallegos, Ms. Angelina Fountain, Ms. Sherry Orman, Mr. David Marcus, Ms. Martha Maser, and Ms. Sheilah Hendrickson, whose efforts, support, and assistance included the typing and editing of over 2500 pages of text.

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

Part 1. Chemicals and Properties of Military Concern Associated with Natural and Anthropogenic Sources

PREFACE

This is the fourth volume of the nine volume report, Evaluation of Military Field-Water Quality. This volume 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 1 addresses the field-water constituents and properties that are associated with natural or anthropogenic sources. 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). Criteria and recommendations for interim standards for radioactivity and selected chemical-warfare threat agents of concern and the risks from exceeding these standards are presented in Part 2 of this volume. These substances are typically 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.

CHAPTER 1. INTRODUCTION

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

ABSTRACT

The purpose of this report is to develop drinking-water standards for field-water constituents and properties of military concern that are naturally occurring or anthropogenically introduced. 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 field-water. Standards are recommended that address both short-term ($\leq$ 7 d) and long-term ($\leq$ 1 y but > 7 d) field-water consumption at rates of 5 and 15 L/d. Turbidity and color are the physical properties of concern because they can adversely impact the organoleptic quality (e.g., taste, odor, or appearance) of field water and thereby lead to reduced water consumption and subsequent involuntary dehydration, which can degrade performance. Total dissolved solids, chloride, magnesium, sulfate, inorganic arsenic, cyanide, the pesticide lindane, and metabolites of aquatic algae and associated bacteria (i.e., geosmin and 2-methylisoborneol) are the chemical constituents of concern because they can be responsible for degrading performance directly as a consequence of their toxic properties and/or indirectly by adversely affecting the organoleptic quality of field water, which can result in reduced water consumption and an increased risk of dehydration.

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INTRODUCTION

Field water supplies used as sources of drinking water for military personnel can contain chemicals from natural and anthropogenic sources or possess physical properties that pose direct or indirect impacts on health. Of particular concern are performance-degrading health effects. To prevent such detrimental effects, field-water-quality standards have been adopted for several water-quality parameters, including turbidity, color, total dissolved solids (TDS), chloride, magnesium, sulfate, arsenic and cyanide (see U.S. Army Technical Bulletins TB MED 229[1] and TB MED 577[2]). However, comprehensive review and revision of the standards has not been performed since the 1960's.

Two important concerns involving the existing standards are whether they include all of the constituents of field water that are of potential concern and whether they are still valid or need to be revised, given the research conducted over the past twenty years since their original adoption. The first concern was addressed in earlier screening assessments we completed to identify organic chemical contaminants,[3] pesticides,[4] and inorganic chemicals and physical properties[5] that could pose adverse health risks based on their occurrence in water supplies, concentrations, and toxicity. Those analyses confirmed that the eight chemical constituents and properties listed above are still relevant and that standards are needed to protect the health of military personnel. We also identified lindane, a commonly used pesticide, and the taste- and odor-causing metabolites (i.e., geosmin and methylisoborneol) of aquatic algae and associated bacteria as additional constituents of concern.

The second issue involving the validity of the current standards is addressed in this report. Specifically, we present reviews and assessments of the potential health effects associated with each of the chemical constituents and properties of interest, define applicable criteria for establishing standards, and then recommend revised or new standards that protect against performance-degrading effects. Finally, we present recommendations for research that can provide data and results for reducing uncertainties related to the standards developed.

FIELD-WATER-QUALITY STANDARDS: BACKGROUND

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. Adverse effects can result from both the toxic and organoleptic properties of field water. Although the direct, toxic effects of dissolved constitutents are a primary concern in the development of standards, involuntary dehydration resulting from the reduced consumption of aesthetically poor water is a concern as well because dehydration can lead to heat illness.[6] Consequently, 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 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 various standards 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, we describe the rationale and basis of the key considerations affecting the analyses supporting the recommended standards.

Water Consumption Rates and Exposure Periods

Maximum water consumption rates for military personnel appear in the Water Consumption Planning Factors Study[7] 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.[8] 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 chemical attack, in particular, is not anticipated; or integrated, in which chemical attack is 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 also 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 the multivolume series titled Evaluation of Military Field-Water Quality (this is Part 1 of Volume 4 of the series). Such daily maximum consumption rates also are 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.[9]

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., ≤ 7 d) and long-term consumption lasting up to one year but exceeding seven days (i.e., ≤ 1 y but > 7 d). Short-term consumption standards for field water are needed because in some battlefield situations access to drinking water meeting long-term consumption standards may be prohibited. However, in the opinion of the U.S. military and civilian experts on the DoD MSG such access is unlikely to be denied for more than seven consecutive days. Long-term consumption standards for field water are applicable to forces deployed in military situations lasting up to one year; in these situations, military personnel would obtain the greatest proportion of their drinking water during that time from military water-purification equipment such as the reverse osmosis water purification unit (ROWPU). The DoD MSG concluded that a one-year duration for long-term field-water-quality standards was sufficient. The rationale for this conclusion is that within a year most of the drinking water consumed by field forces should be provided by properly functioning fixed installations.

Other Considerations

The paramount focus of the research presented in this report is to develop and recommend standards that should 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, dose-reponse relationships for humans were extrapolated from oral-dose data for animals. 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.

Furthermore, the field-water-quality standards contained in this document and recommended for adoption by the Armed Forces of the United States were developed with regard to (1) typical pH values (acidity/alkalinity) of field water, (2) an optimum temperature of field water for consumption by military personnel, and (3) a threshold odor number (TON) of field water that is characteristic of an odor level that military personnel in battlefield situations should find acceptable. Our review of the literature concerning the pH of natural waters, which is contained in Part 3 (Inorganic Chemicals and Physical Properties) of Volume 2 (Chemical Constituents of Military Concern from Natural and Anthropogenic Sources),[5] revealed that typical pH values of natural waters can vary between 5 and 9, and the vast majority of natural waters will have a pH between 6.4 and 8.5. Coincidentally, the later range for pH is consistent with that recommended by the U.S. Environmental Protection Agency (EPA) as a National Secondary Drinking Water Regulation (i.e., 6.5 to 8.5) to minimize adverse effects that excessively high or low levels of pH might have on disinfection processes, as well as on taste and corrosivity.[10] Also, according to TB MED 577,[2] the optimum temperature of drinking water for consumption by military personnel is 60°F plus or minus 10°F (16°C plus or minus 5°C). This preferred temperature for consumption is supported by data presented by Hubbard et al.[11] in a report concerning voluntary dehydration and water alliesthesia (e.g., thirst sensation is positively or negatively influenced by stimuli such as cold or hot temperature of water). Finally, the U.S. EPA[10] indicated that a threshold odor number (TON) of three (as determined by procedures described in Standard Methods for the Examination of Water and Wastewater[12]), which is a National Secondary Drinking Water Regulation, was characteristic of an odor level that most consumers in the general population would find acceptable.

If the pH, temperature, and/or odor of a field-water supply is outside of the levels or ranges that are "tolerable" in terms of palatability and potability, personnel drinking the water may find it aesthetically undesirable. This condition could lead to reduced water consumption, susceptibility to dehydration, and subsequent performance degradation. However, the data available in the literature were not able to support development of standards based on a direct relationship between performance-degrading organoleptic or health effects in military personnel and levels of these properties outside the limits identified as typical, optimum, or acceptable for palatability and potability. The data indicated only that a potential source of drinking water may not be consumed if the pH, temperature, and/or odor of the water were outside these limits, independent of the concentration of any other chemicals or properties present in the water. Consequently, the development of standards that would protect against adverse effects related to potential synergistic relationships between these properties also was not possible.

Moreover, data were virtually absent for determining the potential health consequences or aesthetic impacts from the chemicals and properties of military concern if the pH of field water is outside the limits indicated to be typical of natural waters and considered tolerable for consumption.

Even though there are very little data to define the potential health risks of temperature and pH in field water outside the tolerable limits, temperature and pH are addressed in detail in the literature with respect to their influence on the disinfection of drinking water, especially with regard to the effectiveness of chlorine. According to data presented in a review article by Lippy,[13] the predominant dissociated form of chlorine in water at a pH between 6 and 7.5 is hypochlorous acid (HOCl), which is an effective biocide, but the hypochlorite ion (OCl^-), which is a relatively poor disinfectant and results from the dissociation of HOCl, predominates as pH levels rise from 8 to 10. Therefore, it may be necessary to lower pH if OCl^- predominates, or if the chlorine requirement to achieve adequate disinfection at higher pH levels becomes so great as to produce an objectionable taste. In fact, the recommended standard for pH for long-term consumption (> 7 d) of field water appearing in the latest edition of TB MED 577[2] (i.e., pH between 5 and 9) appears to be based on facilitating adjustments in the amount of chlorine that may be required to maximize disinfection and to minimize potential adverse taste problems. Furthermore, temperature also influences the dissociation of HOCl to OCl^-, but to a much lesser extent than pH,[14] such that the reaction of chlorine with microorganisms is inversely related to water temperature.[13] For example, the latest edition of TB MED 577[2] recommends that the 30-min chlorine residual for adequate disinfection that is applicable to pH levels in water at temperatures at or above 40°F (5°C) be doubled for similar pH levels in water at temperatures less than 40°F (5°C).

Finally, odor can be caused by a variety of different inorganic and organic substances and its control requires knowledge of the nature of the odorous material.[10] Moreover, odor by itself is an aesthetic (i.e., organoleptic) property and not directly related to health effects and because most consumers in the general population would find drinking water containing a TON of 3 to be acceptable,[10] we assume that military personnel under battlefield conditions should find field waters containing a TON between 0 and 3 to be equally palatable and potable for consumption.

Objectives of the Field-Water-Quality Standards

The specific objectives of short- and long-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 greater than for field-water meeting long-term standards. Alternatively, long-term standards should protect against any adverse health effects that could appear during a 1-y period of exposure. Longer-term adverse health effects are not addressed in the recommendations for field-water quality standards. In combat situations longer-term adverse health effects (e.g., carcinogensis, teratogenesis, or latent or chronic effects), are typically not as imminent nor as consequential as a performance decrement induced by immediate (i.e., acute) health effects. Nevertheless, potential chronic effects are identified in discussions accompanying the recommendations 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 similar to male populations. For example, they 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 also are 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

Table 1. Summary of recommended field-water-quality standards and other selected drinking-water standards.

Constituents	Recommended standards[a]				TB MED 229[b]		TB MED 577[c]		QSTAG 245[d]		International[g]			
	[≤ 7 d]		[≤ 1 y]		[≤ 7 d]	[> 7 d]	[≤ 7 d]	[> 7 d]	[≤ 7 d[e]]	[> 7 d[f]]				
	5 L/d	15 L/d	5 L/d	15 L/d	5 L/d	5 L/d	5 L/d	5 L/d	5 L/d[h]	5L/d[h]	US	CAN	EEC	WHO
PHYSICAL PROPERTIES:														
Turbidity (NTU, unless otherwise noted)	1	1	1	1	Reasonably clear	5 units	Reasonably clear	5	5	1	1 to 5[i]	5	4[j]	5
Color (color units, unless otherwise noted)	50	50	15	15	-----	50	-----	50	-----	15	15[k]	15	20[j,l]	15
Total dissolved solids (mg/L)	1600	1000	1000	1000	-----	1500	-----	1500	1500	1500	500[k]	500	400[m,n]	1000
pH	-----	-----	-----	-----	-----	-----	-----	5.0 to 9.0	5.0 to 9.2	5.0 to 9.2	6.5 to 8.5[k]	6.5 to 8.5	-----	6.5 to 8.5
Temperature (°F)	-----	-----	-----	-----	-----	-----	----[o]	----[o]	39.2 to 95	59 to 71.6	-----	59	77	-----
CHEMICAL CONSTITUENTS:														
Chloride (mg/L)	600	600	600	600	-----	600	-----	600	-----	600	250[k]	250	25[m]	250
Magnesium (mg/L)	100	30	100	30	-----	150	-----	150	-----	150	-----	-----	50[j]	-----
Sulfate (mg/L)	300	100	300	100	-----	400	-----	400	-----	400	250[k]	500	25[m]	400
Total inorganic arsenic (mg/L)	0.3	0.1	0.06	0.02	2.0	0.2	2.0	0.2	2	0.05	0.05[i]	0.05	0.05[j]	0.05
Cyanide (mg/L)	6	2	6	2	20	2	20	2	20	0.5	-----	0.2	0.05[j]	0.1
Lindane (mg/L)	0.6	0.2	0.6	0.2	-----	-----	-----	-----	-----	-----	-----	0.004	0.001	0.003
Organoleptic metabolites of algae and associated aquatic bacteria (ng/L)	10	10	10	10	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

Footnotes for Table 1. Summary of recommended field-water-quality standards and other selected drinking-water standards.

[a] 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.

[b] Reference 1.

[c] Reference 2.

[d] Minimum treatment requirements for assuring potability as presented in Table A of Reference 15.

[e] Short-term consumption provisions that according to Quadripartite Standardization Agreement (QSTAG) 245 (Ref. 15) 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] Long-term consumption provisions, which according to QSTAG 245 (Ref. 15), are designed to assure the health and maintain the performance of troops provided their health is good and their rations are adequate.

[g] Reference 16.

[h] For consumption rates exceeding 5 L/d, QSTAG 245 (Ref. 15) states that the permitted level for toxic substances (e.g., arsenic and cyanide) be based on the maximum daily dose that would be ingested at the 5 L/d consumption rate.

[i] Enforceable U.S. primary drinking water regulation.

[j] European Economic Community (EEC) maximum admissible concentration.

[k] Nonenforceable U.S. secondary drinking water regulation.

[l] Measured in units of mg Pt-Co/L.

[m] Guidance level.

[n] Measured as conductivity (μS/cm).

[o] Optimum drinking-water temperature for palatability identified in Reference 2 as being 60°F ± 10°F (16°C ± 5°C), but not specified as a field-water-quality standard.

of U.S. Army Technical Bulletin No. TB MED 577,[2] the most recent version of Quadripartite Standardization Agreement (QSTAG) 245,[15] and cited by Sayre[16] in a review of "International Standards for Drinking Water." The standards for constituents of drinking water that are summarized in Table 1 have been divided into two categories: those related primarily to the physical condition or organoleptic quality (e.g., taste, odor, appearance) of the water and those related to the chemical quality of the water.

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 treatement efficiency attainable by military water-purificiation 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. Finally, a temperature of 60°F $\pm$ 10°F (16°C $\pm$ 5°C), a pH between 5 and 9, and a TON between 0 and 3 represent optimum tolerable limits for these attributes of field water for military personnel. Consequently, standards that are recommended for other chemicals and properties of field water take into consideration the aforementioned optimum limits for temperature, pH, and odor. In fact, a potential source of drinking water may not be consumed if the temperature, pH, and/or odor of the water were outside the optimum limits, independent of the concentration of other chemicals or properties of military concern.

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CHAPTER 2. TURBIDITY AND COLOR

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ABSTRACT

Water quality limits for turbidity and color are accepted generally as aesthetic standards; no evidence indicates that a direct relationship exists between human health effects and turbidity and color in water. However, high levels can make the water objectionable to many individuals, causing them to refuse to drink it. In some situations, these individuals could become susceptible to dehydration, which could result in performance-degrading effects. Additionally, turbidity can affect the efficacy of chlorination thereby increasing exposure to infecticus microorganisms in field water that can pose a significant risk to health.

We present data that relate the percent of military personnel that would drink water with varying levels of turbidity, color, and odor. The data suggest that approximately a third of military personnel might reject field water that meets existing military standards (5 units of turbidity and 50 units of color). However, a turbidity level less than or equal to 1 nephelometric-turbidity unit (NTU) not only would tend to improve the efficacy of disinfection for most infectious microorganisms (the protozoa Giardia and Cryptosporidium are notable exceptions), but also would reduce the percentage of military personnel that may refuse to drink the water and become susceptible to the performance-degrading effects of dehydration to levels as low as about 2%, provided color and odor are absent. Thus, we recommend that the exisiting turbidity standard of 5 units be changed to 1 NTU. We also recommend that the exisiting color standard be changed to 15 color units for long-term ($\leq$ 1-y) exposure and 50 color units for short-term ($\leq$ 7-d) exposure because (1) color is not directly associated with health effects, and (2) these color levels, although noticeable, can be considered tolerable for military populations from an organoleptic or aesthetic standpoint.

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INTRODUCTION

The acceptance of supplied drinking water is a fundamental consideration in the management and control of water quality. Although water quality may be defined in terms of physical, chemical, and bacteriological parameters, the characteristics with the greatest influence on acceptability are those that affect the human senses.[1] These characteristics include turbidity, color, odor, and taste. In this report, we present information on the occurrence, sources, existing standards, analytical techniques, health effects, and public acceptability of turbidity and color. In addition, we recommend standards for turbidity and color in field waters used as drinking-water sources for military personnel.

TURBIDITY

Turbidity in water is caused by suspended material such as clay; silt; finely divided organic and inorganic matter; soluble, colored organic compounds; and plankton and other microorganisms.[2] Turbidity may result from natural processes such as erosion, or it may result from discharge of domestic and industrial waste to surface waters. For example, suspended material derived from mining, dredging, logging, pulp and paper manufacturing, and other industrial activities will contribute to water turbidity.[3] In fact, increased stream turbidity commonly results from soil disturbances due to events such as improper road location, which in the past typically has been associated with forestry operations; naturally occurring landslides caused by steep or unstable slopes; and catastrophic fires that can expose soil to runoff.[4] Coincidentally, such events are comparable to those that might occur during field-combat situations.

The turbidity of water is an expression of the optical property that causes light to be scattered and absorbed by suspended material. Thus, the degree of turbidity can be measured either by reduction in the amount of light transmitted through a column of water (spectrophotometry) or by the amount of light reflected by the suspended particles (nephelometry). The degree of turbidity measured using these methods is not equal to the amount of suspended solids; it is only an expression of an effect of suspended solids on the optical characteristics of the water. The importance of turbidity as a field-water-quality parameter is related to its organoleptic property of unfavorably affecting the appearance of water and to its potential for adversely affecting disinfection processes, as will be discussed later.

The turbidity standards that are currently applied to military water supplies are presented in Table 1. We presume that the units in Table 1 are nephelometric-turbidity units (NTUs) because the minimum treatment requirements for turbidity for short-term and long-term consumption, which are contained in the most recent edition of the quadripartite agreement between American, British, Australian, and Canadian military forces, are given in terms of NTUs and correspond to those in Table 1 for fixed installations.[8]

ANALYTICAL METHODS

Several methods to measure turbidity are presently used by operators at municipal water-treatment facilities. These methods include use of the Jackson Candle turbidimeter, nephelometer, spectrophotometer, visual comparison with standards, and operator judgment. The two approved methods contained in the 15th edition of Standard Methods for the Examination of Water and Wastewater[2] use the Jackson candle turbidimeter and the nephelometer.

Historically, the most frequently used instrument for the determination of turbidity has been the Jackson turbidimeter; however, because the lowest turbidity value that could be measured directly on this instrument was 25 Jackson turbidity units (JTU), other methods (e.g., nephelometric and visual comparison) are used. A detailed discussion of the apparatus and procedures for determining JTUs and NTUs is presented in the 15th edition of Standard Methods for the Examination of Water and Wastewater.[2]

Table 1. Turbidity standards currently applied to U.S. military water supplies.

Water source	Short term	Long term
Field supplies	Reasonably clear[a]	5 units[a]
Fixed installations	5 units[b]	1 unit[c]

[a] From U.S. Army.[5]

[b] Corresponds to 1962 drinking-water standard for turbidity established by U.S. Public Health Service.[6]

[c] Corresponds to the 1975 National Interim Primary Drinking Water Regulations for turbidity, established by U.S. Environmental Protection Agency.[7]

As described in the previously mentioned book,[2] turbidity measurements by the candle turbidimeter are based on analysis of the light path of a standard candle flame viewed through suspended material. The longer the light path, the lower the turbidity. As noted previously, the lower limit of the candle turbidimeter is 25 JTUs. Because turbidity in treated waters generally is less than 25 JTUs, indirect methods are employed to estimate these turbidity values. For example, a visual comparison with prepared turbidity standards may be employed.

At present, nephelometry is the primary method used for measuring turbidity. As described in Standard Methods,[2] this method is based on a comparison of the intensity of light scattered by the sample under defined conditions with the intensity of light scattered by a standard reference suspension under the same conditions. The higher the intensity of scattered light, the higher the turbidity. Formazin polymer is used as the standard reference suspension for turbidity. The turbidity of a specified concentration of formazin is defined as 40 NTU and has an approximate turbidity of 40 JTU. Therefore, nephelometric-turbidity units based on the formazin standard will approximate units from a candle turbidimeter.

Two other methods are currently used by the U.S. Army to determine turbidity.[9] One method employs a white porcelain cup with a black enameled dot at its bottom. If the black dot cannot be seen when the cup is filled to the top with raw water, the turbidity is considered to be greater than or equal to 100 turbidity units (TU). Alternatively, the turbidity is considered to be less than 100 TU if the black dot at the bottom of the cup is visible. The other method employed by the U.S. Army involves the use of a turbidimeter to visually compare a water sample with a calibrated stock suspension.

HEALTH EFFECTS

We reviewed the literature to determine whether a relationship could be documented between disease and suspended particles in water. Several studies provided insight to this relationship. The studies are discussed next in terms of information dealing with a direct relationship between turbidity and disease, information covering turbidity and its effect on disinfection efficiency, and information covering the aesthetic quality of water.

Relationship Between Turbidity and Disease

Studies on the direct relationship between turbidity and disease were reviewed and are summarized below.

1. In 1948, Neefe et al.[10] added 40 to 50 mg of feces containing the causative agent of infectious hepatitis to one liter of distilled water. They treated the water specimens by using various techniques that include coagulation, particulate-activated-carbon treatment, filtration, and chlorination. These specimens were then fed to human volunteers. The results indicated that ingestion of untreated water resulted in a 67% average incidence of hepatitis. Water that was disinfected to a total-chlorine residual of 1.1 mg/L after 30 min caused hepatitis in two of five volunteers. Finally, a specimen of water that was first coagulated, filtered, and then disinfected to the same chlorine residual produced no hepatitis in five volunteers. This experiment was repeated with seven additional volunteers, and again no infectious hepatitis occurred.

2. Chang et al.[11] showed that nematodes could ingest enteric bacterial pathogens, as well as viruses, and that a small percentage of the organisms could survive for 24 h at 25°C. In addition, they showed that nematode-borne organisms were completely protected against chlorination even when more than 90% of the carrier worms are immobilized.

The importance of studies 1 and 2 relative to the direct relationship between turbidity and disease is questionable; they are discussed here only because they are referenced frequently by other authors reporting on this topic.

3. Data from three water-treatment facilities that treated surface water were analyzed by Walton.[12] Coliform bacteria were detected in the chlorinated water at only one facility. This facility generally had turbidities less than 10 TU, but occasionally turbidities as great as 100 units were found.

4. Sanderson and Kelly[13] studied an impounded water supply that received only chlorination treatment. Water samples consistently yielded confirmed coliform organisms and contained turbidities ranging from 4 to 84 units. They concluded "...coliform bacteria were imbedded in particles of turbidity and were probably never in contact with the active agent. Thus, it would be essential to treat water by coagulation and filtration to nearly zero turbidity if chlorination is to be effective."[13]

5. Hudson,[14] using Walton's[12] data as well as his own, related the incidence of infectious hepatitis to turbidity in the finished drinking water for several cities in the United States. A summary of his data analysis is shown in Table 2. Hudson concluded that "...low rates of virus disease occur in cities where the water treatment operators aim to produce a superior product rather than a tolerable water."[14]

6. In 1963, an analysis of water in the San Andreas reservoir in San Francisco, California, was conducted by Tracey et al.[15] The results showed that 33% of all coliform samples had five positive test tubes (e.g., presence of coliform indicated by gas production

Table 2. Relationship between filtered-water quality, free-chlorine residual, and hepatitis incidence, determined from data collected in 1953.[a]

Average turbidity (TU)	Final chlorine residual (mg/L)	Hepatitis (cases/100,000 people)
0.15	0.1	3.0
0.10	0.3	4.7
0.25	0.3	4.9
0.2	--	8.6
0.3	0.4	31.0
1.0	0.7	130.0

[a] From Hudson.[14]

visible in specially designed test tube), in spite of the presence of a chlorine residual. Additionally, the results indicated that during the period of greatest coliform persistence, the turbidity of the water ranged from 5 to 10 TU.

7. In laboratory studies, Robeck et al.[16] showed that floc breakthrough from a granular filter, sufficient to cause a turbidity of less than 0.5 TU, was usually accompanied by a virus breakthrough.

Although the results of all these studies are interesting, we must be cautious of concluding too much from these findings. Our review of the literature did not reveal a direct relationship between disease and turbidity in water. However, the results do indicate that a low-turbidity water is important to have prior to disinfection.

Disinfection Efficiency

The rationale behind emphasizing low turbidity levels for potable water is based on the interference of particles with disinfection chemicals. We reviewed several studies that support this rationale. The following is a summary of these studies.

1. Symons and Hoff[17] reported the results of a study that evaluated the inactivation of poliovirus-1 in several different suspensions: (1) demand-free (virus in a chlorine demand-free suspension), (2) alum-flocculated, (3) bentonite-adsorbed, and (4) cell-associated. In each suspension, chlorine was used as the disinfecting agent. The results indicated that alum and bentonite turbidity (inorganic), ranging from 4.2 to 5.5 TU, had no effect on virus inactivation (disinfection efficiency). The demand-free

virus-inactivation rates, with turbidity of 0.2 unit, were similar to the bentonite and alum-flocculated inactivation rates. Finally, turbidity associated with cell culture (debris associated with virus culture) of 1.4 units reduced virus-inactivation rates and thereby protected the viruses from chlorine disinfection.

2. Scarpino et al.[18] reported a study that evaluated the ability of suspended matter and viral aggregation to affect the efficiency of chlorine dioxide disinfection. The results of the study indicated that bentonite turbidity (inorganic) ranging from 0.5 to 16 NTU, and increasing temperatures of 5 to 25°C, slightly decreased the efficiency of chlorine dioxide disinfection. The study demonstrated that a bentonite-adsorbed virus with a turbidity of ≤5 NTU was protected to 11.4% (88.6% unprotected) and the same virus with a turbidity between 5 and 17 NTU was protected to 24.8% (75.2% unprotected). It was also reported that cell-associated viruses with turbidities ranging from 1.1 to 3.1 NTU had no effect on the efficiency of chlorine dioxide disinfection. A reevaluation of Scarpino's data indicates that the disinfection efficiency at turbidities below 10 NTU appears to be a function of temperature (in the ambient range) rather than turbidity (i.e., increasing temperature increases efficiency), and that above 10 NTU, turbidity appears to play a role in decreasing disinfection efficiency.

3. Sproul et al.[19] investigated the effect of suspended particles on ozone disinfection of enteric bacteria and viruses adsorbed to or incorporated into these materials. The particles were fecal material, HEp-2 cells, alum-oxide floc, and bentonite clay. The results indicate that HEp-2 cells and fecal material turbidity (organic) of 5 NTU decreased ozone disinfection efficiency; the bentonite and alum-oxide turbidity (inorganic), ranging from 1 to 5 NTU, did not affect significantly the ozone disinfection efficiency.

4. LeChevallier et al.[20] studied the interrelationships between elevated turbidity levels and the efficiency of chlorination in drinking water for six watersheds in Oregon. The results indicated that the magnitude of coliform masking in the membrane-filter technique increased approximately 40% in water samples with more than 5 NTU. Additionally, a model was developed that indicated that an increase in turbidity from 1 to 10 NTU in the surface-water supply would result in an eight-fold decrease in the efficiency of disinfection. Finally, the results indicated that the turbidity was primarily organic material.

5. Budde et al.[21] investigated the bactericidal efficiency of three disinfectants: chlorine, iodine, and ozone. In general, the results indicate that an increase of 2 JTU increased the required dose of iodine by 1 mg/L, chlorine by 0.2 mg/L, and ozone by approximately 3 mg/L. Review of the data indicates that the turbidity was primarily organic material.

In general, the results of the above studies indicate that turbidity values above 5 NTU, caused by organic material, decreased disinfection efficiency, whereas inorganic sources of turbidity did not. Additionally, because chlorine demand was directly related to organic turbidity, the chlorine demand might be an appropriate means to determine whether turbid water supplies would decrease chlorine efficiency and thereby increase the chances for biological pathogens to reach the consumer. However, the cysts of the protozoa Giardia and Cryptosporidium are especially resistant to disinfection, and Cryptosporidium cysts may be even more resistant to disinfection than Giardia cysts.[22,23] These pathogenic microorganisms, which can cause severe diarrheal illnesses[22,23] (e.g., a severe Cryptosporidium infection could cause profuse diarrhea and a corresponding fluid loss of up to 10 L/d[24]), may even be present in unfiltered natural waters with turbidity levels less than or equal to 1 NTU.[24,25] The cysts of Cryptosporidium may even resist disinfection in such low turbidity water.[22,24] Nevertheless, limiting turbidity to 1 NTU or less should optimize disinfection efficiency for most other pathogenic microorganisms by minimizing the interfering effect of turbidity, specifically organic turbidity, on disinfection processes and by preventing any turbidity from shielding microorganisms from the disinfectant.

Acceptability as a Function of Turbidity

In 1972, Harris[1] completed a study designed to systematically relate combinations of turbidity, color, and odor values to public acceptability of water (from 0 to 100%). In the study, he obtained acceptability ratings from three consumer populations, each with different sources for drinking water: bottled water, filtered tapwater, and unfiltered tapwater. For this assessment, Harris prepared 125 water samples consisting of all possible combinations of five turbidity values (0, 5, 10, 20, and 40 TU), five color values (0, 15, 30, 50, and 70 color units), and five odor values (1, 3, 12, 50, and 200 threshold odor numbers). These 125 samples were then separated randomly into nine sample sets: eight groups of 14 samples and one group of 13 samples ([8 x 14] + [1 x 13] = 125). From each of the three consumer populations, 180 people were selected corresponding to a total of 540 people (3 x 180 = 540). These respondents were selected from all age groups and both sexes to minimize effects of biasing factors. Each of the three representative groups of 180 people was divided into nine subgroups of 20 (9 x 20 = 180); one subgroup from each representative group reviewed each of the nine sample sets. In this way, 60 people (3 x 20 = 60) assigned water acceptability ratings to each of the samples of a sample set. Therefore, a total of 7500 acceptability ratings were recorded ([60 x 8 x 14] +

Table 3. Action-tendency scale for rating water on the basis of color, turbidity, and odor.

Rating	Statement
1	I would be very happy to accept this water as my everyday drinking water.
2	I would be happy to accept this water as my everyday drinking water.
3	I am sure that I could accept this water as my everyday drinking water.
4	I could accept this water as my everyday drinking water.
5	Maybe I could accept this water as my everyday drinking water.
General Population	
6	I don't think I could accept this water as my everyday drinking water.
Military Population	
7	I could not accept this water as my everyday drinking water.
8	I could never drink this water.

[60 x 1 x 13]). In assessing each sample, the respondent observed and smelled the sample, which was presented in a clear glass 6-ounce bottle and presumably at a temperature typical of tap water (only visual and olfactory examination was permitted because a pilot study indicated that essentially the same acceptability rating distributions would be obtained if respondents were requested to examine the water sample in a drinking glass and to taste the sample; consequently, the simpler method was employed). Next, the respondent indicated the degree to which he or she could accept the water by selecting the appropriate rating on the action-tendency scale shown in Table 3.

According to Harris,[1] the borderline between acceptance and rejection for the general population was located between statement 5 on the rating scale ("Maybe I could accept this water as my everyday drinking water") and statement 6 ("I don't think I could accept this water as my everyday drinking water"). The action-tendency scale is a continuum reflecting the degree of acceptance or rejection. This continuum permits the respondents to reflect more accurately their feelings about consuming the water sample.[1]

Harris prepared frequency distributions of ratings for each of the 125 combinations of turbidity, color, and odor values for each water sample and for the total number of responses. An example of one such frequency distribution is shown in Table 4. To transform the rating responses to acceptability percentages, the responses above the

Table 4. Distribution of respondent action-tendency ratings for three different water sources having a turbidity of 5 TU, a color of 15 units, and a threshold odor number of 3.[a,b]

Rating	Water source (number of respondents) Bottled water (N=20)	Filtered tap water (N=20)	Unfiltered water (N=20)	Total (N=60)
1		2	2	4
2		2	3	5
3	1	2	3	6
4	2	3	5	10
5	11	6	2	19
General Population				
6	2	4	3	9
Military Population				
7	1		2	3
8	3	1		4

[a] From Standard Methods.[2]

[b] Turbidity, color, and odor values as specified by U.S. Environmental Protection Agency.[7,26]

acceptance/rejection borderline must be summed and divided by the total responses (N). For example, the acceptability percentage for the general population based on the data for water having a turbidity of 5 TU, a color of 15 units, and a threshold odor number* of 3 (see Table 4) is 73% (44 of 60).

The calculated acceptability percentages for all 125 combinations of turbidity, color, and odor values were then plotted by Harris, resulting in five charts.[1] Because use of the charts for our purposes was cumbersome, we reanalyzed Harris's raw data (see

* According to Standard Methods,[2] the threshold odor number (TON) is determined by diluting a sample with odor-free water until the least definitely perceptible odor is achieved and then computing the TON using the following equation:

TON = (mL of sample + mL of odor-free water)/(mL of sample).

Appendix A). From our reanalysis of Harris's raw data we derived the following multiple regression equation (see Appendix B):

$$A = 86 - 0.5(C) - 1(T) - 0.1(S) \quad , \qquad (1)$$

where

A = percentage of population rating water acceptable,
C = color units,
T = turbidity units,
S = threshold odor number.

Use of this statistical approach allows us to obtain a mathematical description of the relationship between the variables in question (i.e., color, turbidity, odor, and acceptability). The mathematical relationship derived provides a tool that can be used easily by water-quality managers to evaluate drinking water supplies for consumer acceptability. We believe Harris's raw data were obtained using a well developed and valid methodology applicable to the statistical requirements of this regression analysis. Harris's methodology is discussed in detail in his report.[1]

We plotted the acceptability as predicted by Eq. 1 and Harris's data as the observed acceptability; the results are shown in Fig. 1. Figure 1 indicates that Eq. 1 acts as a reasonable predictor of Harris's observed data. Equation 1 has a multiple-correlation coefficient (R) of 0.891, indicating that approximately 80% ($R^2 = 0.794$) of the variation in the population's acceptance of drinking water is explained jointly by color, turbidity, and odor. Furthermore, Eq. 1 has a standard error of 10.2%, indicating minimal variation from observed acceptability data.

To evaluate changes in acceptability associated with changes in turbidity, the color and odor values in Eq. 1 were set at a constant value of 50 color units and 3 odor threshold units. These values are consistent with the existing military standard[5] and the 1962 public-health odor standard.[6] A two-dimensional plot of the percentage of the population that will judge water acceptable, based on the level of turbidity, is shown in Fig. 2. At 5 TU, which is the military standard, estimates show that 56% of the general population considers the water acceptable. This means that approximately 44% of the general population indicated that they "didn't think they could accept the water as their everyday drinking water" (see Table 3). According to Eq. 1, approximately 14% of the population

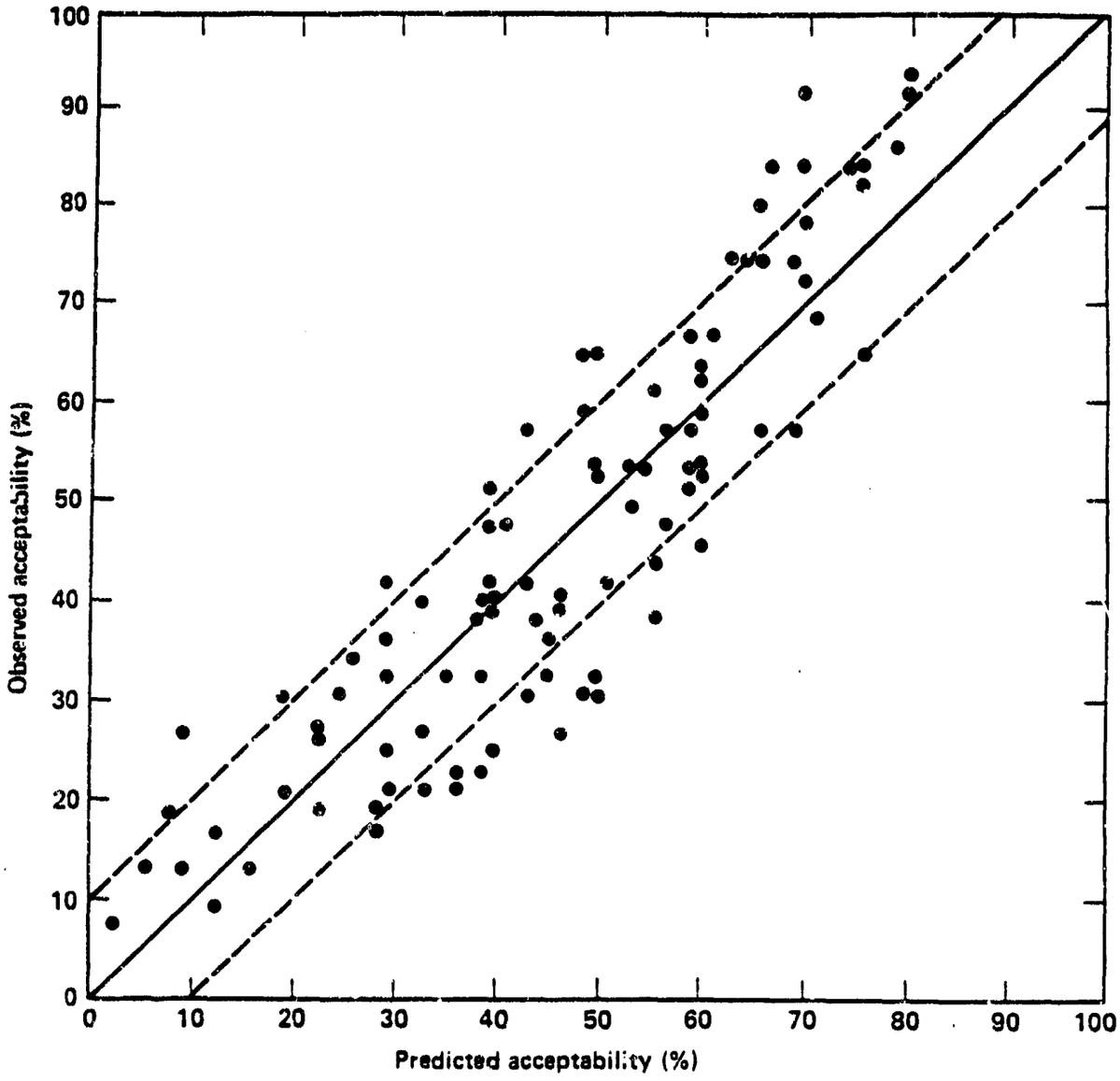

Figure 1. Relationship between observed acceptability and acceptability predicted from multiple regression equation.

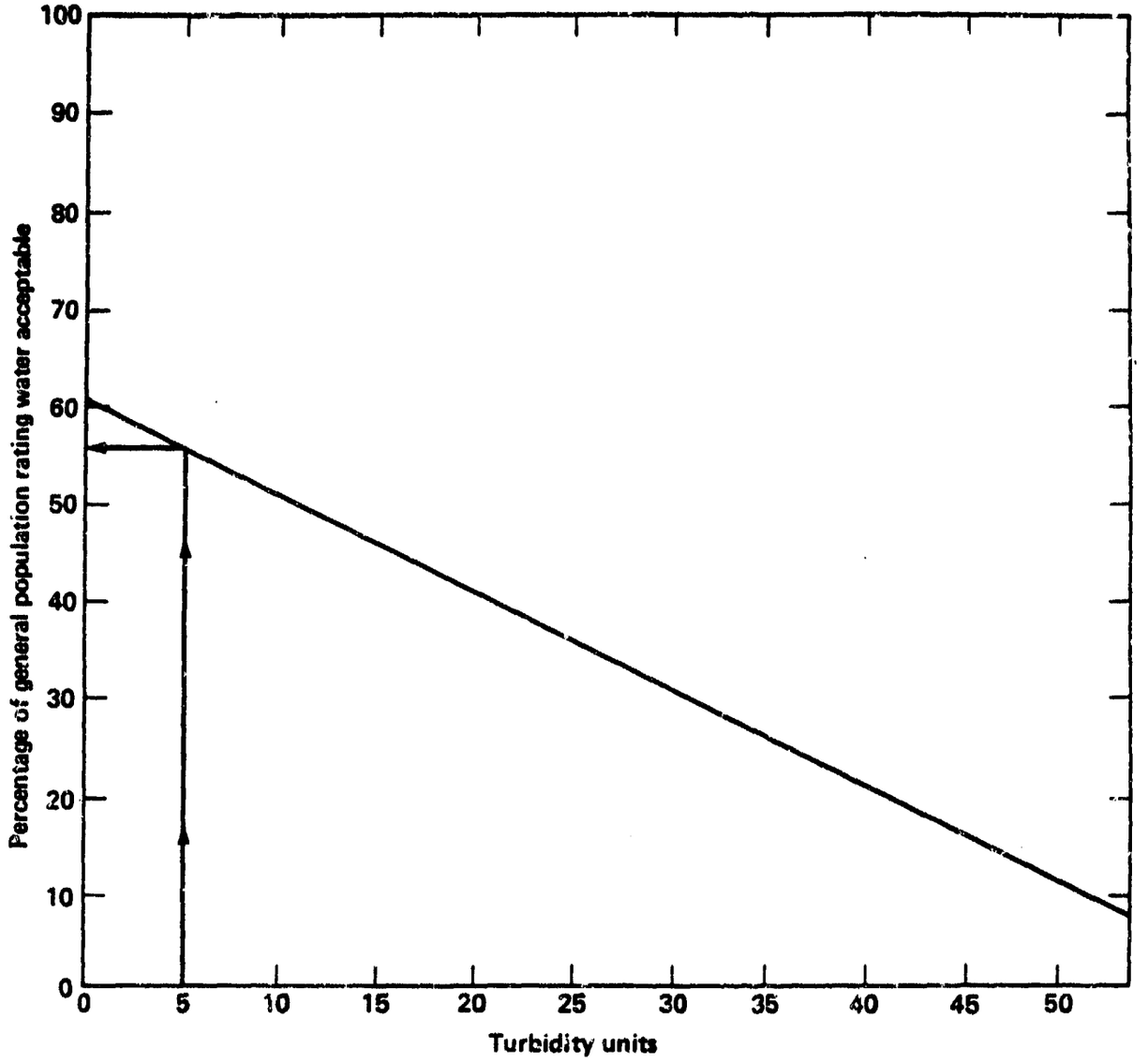

Figure 2. Percentage of the general population that will rate water acceptable, based on turbidity, when color is fixed at 50 color units and threshold odor number is fixed at 3.

would reject the water at zero color, turbidity, and odor levels. This indicates that a high level of background rejection exists. The rejection level may result from constraints within Harris's methodology that are discussed in this report.

DEVELOPMENT OF RECOMMENDATIONS FOR STANDARDS

To develop a recommended standard for turbidity, we make the following assumptions based on the previous discussion.

- Turbidity is a nonspecific water-quality parameter.
- Turbidity is a measure of water-treatment effectiveness.
- Evidence for a direct relationship between disease and turbidity levels in water is mostly anecdotal and tenuous.
- The relationship between turbidity and disinfecting capability of chlorine and other chemical agents for most pathogenic microorganisms depends more upon the type of turbidity (organic or inorganic) than the amount.
- Inorganic turbidity probably has no bearing on the potential protection of pathogens, even though organisms (e.g., viruses) can adsorb onto inorganic material, whereas organic turbidity interferes with disinfection efficiency, thereby potentially protecting the adsorbed organisms.
- In practice, water with less than 5 NTU is more readily disinfected than water having more than 5 NTU, and for most microorganisms water with a turbidity level less than or equal to 1 NTU may even be more readily disinfected than water with turbidity of 5 NTU, depending on the composition of the turbidity (i.e., organic or inorganic). This is particularly true when turbidity is related to chlorine demand.
- Acceptability and attitude responses can be related to turbidity levels by use of psychometric rating scales.
- Detectable turbidity does not make the water undesirable to all consumers.

To develop a recommended standard for turbidity, one additional assumption, not based on the previous discussions, needs to be made.

- Military levels of acceptability may not be equivalent to civilian levels of acceptability because military populations may not be as sensitive as the general population.

Based on this last assumption, the line between acceptance and rejection for the military population is shifted from between rating statement 5 and 6 to between statement 6 and 7 (Table 3). Table 4 indicates that modifying the acceptance/rejection borderline in the aforementioned manner increases the acceptability percentage for this example by approximately 15%. The example presented in Table 4 represents the responses of individuals from each consumer population to water containing turbidity, color, and odor as specified by drinking water standards of the U.S. Environmental Protection Agency.[7,26] Frequency distributions of responses to other combinations of turbidity, color, and odor were not presented by Harris. Therefore, we assume that the 15% difference in acceptance we obtained from modifying the acceptance/rejection borderline in Table 4 is applicable to frequency distributions of responses to all other combinations of turbidity, color, and odor. As previously discussed, when the borderline is between statement 5 and 6, the acceptability percentage is 73% (44 of 60); however, moving the borderline to lie between statements 6 and 7 increases the acceptability percentage to 88% (53 of 60).

By adjusting the general-population curve given in Fig. 2 by 15%, we derive the relationship between the turbidity and acceptance by military personnel as shown in Fig. 3. Figure 3 indicates that at a turbidity level of 5 TU (color = 50 color units and threshold odor number = 3), approximately 64% of the military population would accept the water, whereas 36% would reject it. At a turbidity level of 1 TU (color = 50 color units and threshold odor number = 3), approximately 69% of the military population would accept the water, whereas 31% would reject it. Review of these values indicates that reducing turbidity from 5 TU to 1 TU results in a 5% increase in acceptability. This increase is small because the turbidity value is small to begin with, even though a unit change in turbidity would introduce the greatest change in acceptability because its multiple regression coefficient is the largest.

Finally, review of Fig. 3 indicates that at a turbidity value of zero units (color = 50 color units and threshold odor number = 3), approximately 70% of the military population would accept the water, whereas 30% would reject it. These results, along with those previously mentioned, imply that between 30 to 36% of the troops would refuse to drink the water at low levels of turbidity. Thus, in certain situations (e.g., desert environments), these troops could become susceptible to dehydration, which could result in performance-degrading effects. Note that for a reduction from 5 to 1 TU, when color is fixed at 50 color units and the threshold odor number is fixed at 3, (i.e., considered acceptable to most consumers according to the U.S. Environmental Protection Agency[26]), the rejection level decreases by 5%. Consequently, at a turbidity level of 1 TU

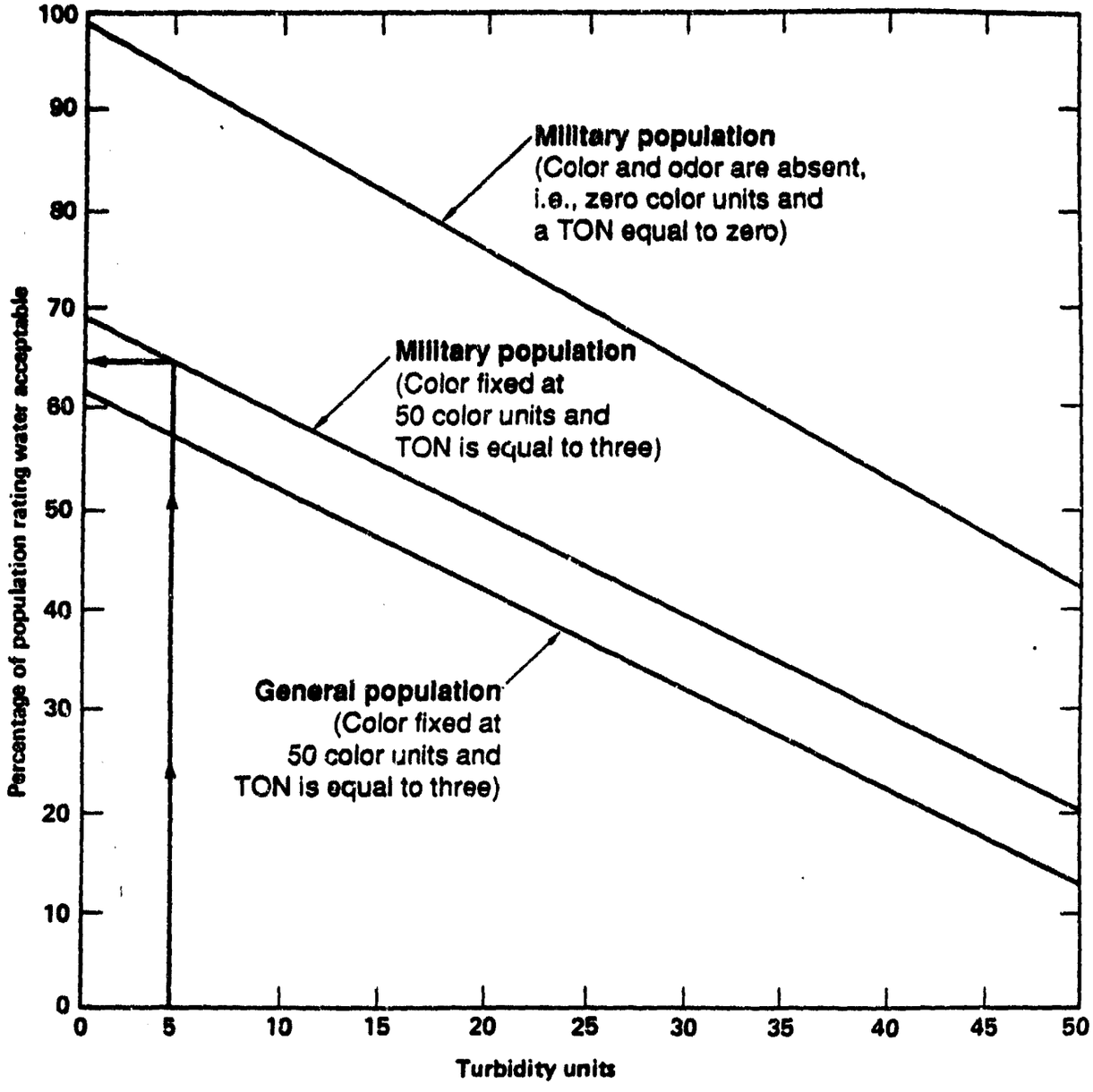

Figure 3. Comparison between military and general populations rating water acceptable based on turbidity.

(color = 50 color units and threshold odor number = 3), a rejection level of 31% remains, which is controlled by several factors. These factors include levels of background rejection (i.e., rejection at color = 0 color units, turbidity = 0 TU, and threshold odor number = 0), implementation of mandatory water-consumption regulations, and modification of the color variable that has the next larger coefficient in Eq. 1. Relative to background levels (color = 0 color units, turbidity = 0 TU, and threshold odor number = 0), the rejection level for the general population was 14% (i.e., 100 - 86) = 14). If this level is adjusted to represent the military population, it is reduced to 1.1% [i.e., 100 - (86)(1.15) = 1.1]. Therefore, when color is fixed at 50 color units, turbidity is 1 TU, and the threshold odor number is fixed at 3, a major part of the remaining rejection level of approximately 30% is controlled by the color variable. Furthermore, if turbidity is 1 NTU and color and odor are absent or are at levels that cannot be perceived, then about 98% of the exposed military population will find the water to be organoleptically acceptable (see Fig. 3).

Analysis of the color variable is discussed in the color section of this report. Implementation of mandatory consumption regulations may reduce the rejection level; however, data do not exist to evaluate this factor.

RECOMMENDATIONS FOR TURBIDITY STANDARDS

The evidence related to the health effects of turbidity is generally anecdotal and tenuous. In this regard, the impact of turbidity on the efficiency of chlorination appears to be more a function of the chlorine demand of the turbidity than the NTU value and the nature of the particles should be considered. Turbidity is accepted primarily as an aesthetic standard; the military-acceptability curve indicates that a significant percentage of the population would reject the water at the present standard. However, this rejection appears to be due to the color standard and not to the turbidity standard. Therefore, the existing long-term standard of 5 TU appears to be reasonable. In fact, the proposed Surface Water Treatment Rule of the U.S. Environmental Protection Agency, published in the Federal Register on November 3, 1987,[27] basically would allow a surface drinking-water source to go unfiltered if it could be demonstrated that the turbidity of the water prior to disinfection does not exceed 5 NTU; however, brief periods of turbidity above 5 NTU may even be allowed because of unusual conditions.

Although the 5 NTU limit may be acceptable for domestic water supplies, we recommend a turbidity level of 1 NTU as the field-water-quality standard for military populations. One reason for this recommendation is that the types of infectious

microorganisms in developing countries that can cause performance-degrading health effects in military populations can differ from those likely to occur in natural waters in the United States or other developed countries. Consequently, natural immunities to such microorganisms will not have had time to develop in a newly exposed military population and such microorganisms may represent a greater risk to military performance than those encountered in the developed countries. Thus, there is an increased need to reduce turbidity levels to ensure that disinfection of the microorganisms is effective. Futhermore, even though a turbidity level of 1 NTU in unfiltered drinking water does not guarantee that water containing the cysts of Giardia and Cryptosporidium can be disinfected, turbidity at levels equal to or less than 1 NTU will improve the efficiency of disinfection for most other infectious microorganisms. In fact, cysts of Giardia and Cryptosporidium may be removed only by filtering water to turbidity levels less than or equal to 0.1 NTU,[24,25] but the effectiveness of such turbidity removal followed by disinfection or as a surrogate for disinfection should be verified. Another consideration in the adoption of a 1 NTU limit is that it would minimize the number of military personnel that would refuse to drink water because of the presence of noticeable turbidity and thereby reduce the likelihood of their becoming dehydrated--especially in hot, arid environments.

COLOR

Color in water may result from the presence of natural metallic ions (iron and manganese), humus and peat materials, plankton, weeds, and industrial wastes.[2] The term "true color," in water-treatment practice, means the color of water remaining after the turbidity has been removed. The term "apparent color" includes color resulting from substances in solution as well as suspended materials. The color of water with low turbidity is basically the same as that of clear water.[3] The color standards that are currently applied to military water supplies are presented in Table 5.

ANALYTICAL METHODS

Several methods to measure color are presently used by operators of municipal water-treatment facilities. These methods include visual comparison, spectrophotometry, and tristimulus filter. All three methods and the applicable apparatus and procedures are discussed in detail in Standard Methods.[2] Our summary of these methods follows, along with a brief description of the technique currently used by the U.S. Army.

Table 5. Color standards currently applied to U.S. military water supplies.

Water source	Short term	Long term
Field supplies	--	50 units[a]
Fixed installations	15[b]	--

[a] From U.S. Army.[5]

[b] Corresponds to 1962 drinking-water standard for color established by U.S. Public Health Service.[6]

As described in Standard Methods,[2] color is determined by visual comparison of the water sample against known values of color in previously standardized solutions. This comparison may also be made with special, properly calibrated, colored glass disks. The unit of color considered as a standard is the color produced by the platinum-cobalt method of measuring (one color unit = 1 mg/L of platinum in water). The results, however, are expressed as units of color, and not mg/L.

The platinum-cobalt standard method is not convenient to use in the field. Standard Methods[2] describes a procedure for comparing glass disks calibrated to correspond to colors on the platinum scale; the disks are used in standard field practice for color determinations.

In the spectrophotometric method, the color of a filtered sample is expressed in terms that describe the sensation realized when viewing the sample.[2] The hue (red, green, yellow, etc.) is designated by the term "dominant wavelength," the degree of brightness by "luminance," and the saturation (pale, pastel, etc.) by "purity."[2] These values are determined from the light-transmission characteristics of a filtered water sample by means of a spectrophotometer.

In the tristimulus-filter method, three special light filters are combined with a specific light source and photoelectric cell in a filter photometer to obtain color measurements. As described in Standard Methods,[2] the percentage of tristimulus light transmitted by the solution is determined for each of the filters; then these values are converted to trichromatic coefficients and color characteristics.

In all the methods, turbidity interferes with the measurement of true color. Therefore, turbidity should be removed (e.g., by filtration) to assure accurate measurement of color. Otherwise, color should be reported as "apparent" color.[2]

The U.S. Army currently employs a color comparison method[9] similar to the one described in Standard Methods[2]; it uses properly calibrated, colored glass disks. In this procedure, circular disks containing calibrated shades of glass are inserted into a color comparator along with the sample. The disk is then rotated until the color of the disk matches the color of the sample; the number assigned to the calibrated glass is recorded as the color-unit value for the sample.

HEALTH EFFECTS

We reviewed the literature to determine whether a relationship between disease and color in water could be documented. Such a relationship could not be substantiated. In general, color is aesthetically undesirable; also, it may dull clothes, or stain food and fixtures. Additionally, an indirect association is implied based upon knowledge that color may be related to naturally occurring organic compounds that react with chlorine, sometimes producing halogenated organic compounds that could be carcinogenic. From the standpoint of aesthetics, the Harris data,[1] previously discussed in the turbidity section, provide relevant information that can be used to estimate the acceptability of drinking water affected by color.

To evaluate changes in acceptability associated with changes in color, the turbidity and odor values in Eq. 1 were set at a constant value of 5 TU and a threshold odor number of 3. These values are consistent with the military's existing turbidity standard[5] and the 1962 public-health odor standard.[6] As a result, we developed a two-dimensional plot of the percentage of the general population that would accept water on the basis of its color content (Fig. 4). At 15 color units, which is the 1962 standard established by the U.S. Public Health Service, the percentage of the general population rating the water acceptable is approximately 73%. This means that approximately 27% of the general population indicated that they "didn't think they could accept the water as their everyday drinking water" (Table 3).

DEVELOPMENT OF RECOMMENDATIONS FOR STANDARDS

To develop a recommended standard for color, we make the following assumptions based on the previous discussion.

- Color is a nonspecific water-quality parameter.
- It is impossible to state that a given color value will have any impact on health.

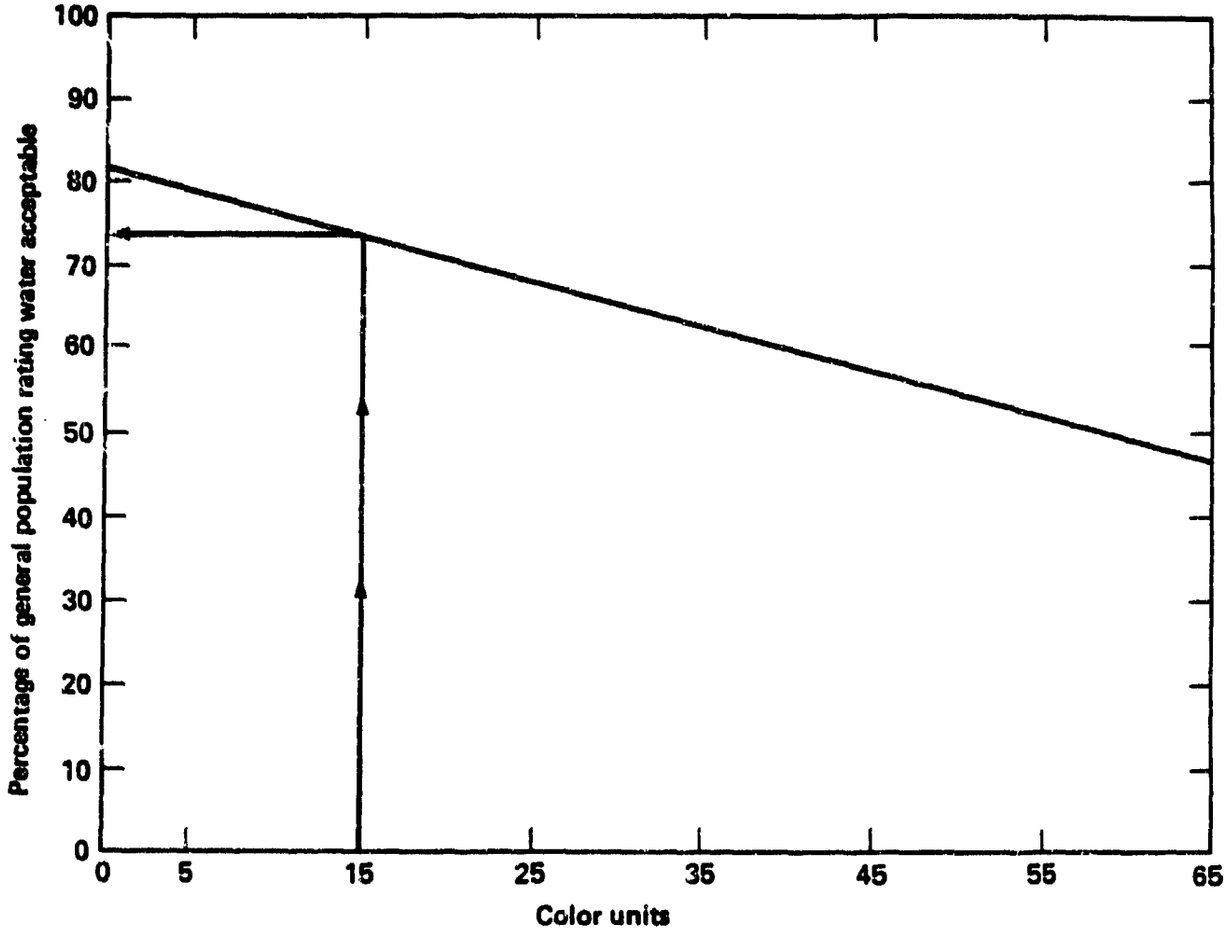

Figure 4. Percentage of general population rating water acceptable on basis of color, when turbidity is fixed at 5 TU and threshold odor number is fixed at 3.

- Color is generally accepted as an aesthetic standard.
- Acceptability and attitude responses can be equated to color levels, using psychometric rating scales.
- Detectable color does not make the water undesirable to all consumers.

One additional assumption, not based on the previous discussion, is made to develop a standard for color.

- Military levels of acceptability may not be equivalent to civilian levels of acceptability because military populations may not be as sensitive as the general population.

Based on this assumption, the borderline between acceptance and rejection for the general population is shifted from between rating statement 5 and 6 to between statement 6 and 7 (Table 3), representing the military population. Harris's data[1] concerning the frequency distribution of respondent action-tendency ratings for color, turbidity, and odor in water (Table 4) indicate that this adjustment modifies the acceptability percentage by approximately 15%. Adjusting the general-population-acceptance curve by 15%, in accordance with the assumptions previously explained in the turbidity section of this report, results in the military-population-acceptance curve shown in Fig. 5. Figure 5 indicates that at the present military color standard of 50 color units, approximately 64% of the military population would accept the water and 36% would reject it. Therefore, these figures imply that those troops refusing to drink the water may suffer from dehydration and subsequent degradation of performance. If the color standard were set at 15 units, approximately 84% of the military population would accept the water and 16% would reject it. A reduction in the rejection level of 20% is achieved by setting the color standard at a more stringent level. Furthermore, the level of rejection will be even lower if turbidity is only 1 NTU, the level recommended as the standard for field water. Note that the 16% military rejection level represents rejection at color, turbidity, and odor values of 15, 5, and 3, respectively, the existing drinking-water standards established by the U.S. Environmental Protection Agency for the general population.[7,26] Furthermore, because the color of water does not pose any direct health risk, color levels of 50 color units and 15 color units for short- ($\leq$ 7-d) and long-term ($\leq$ 1-y) exposure to field water, respectively, can be considered safe. With regard to aesthetic responses to color in water, the U.S. Environmental Protection Agency indicates that many individuals in the general population would not detect a color level of 3 color units and would be more

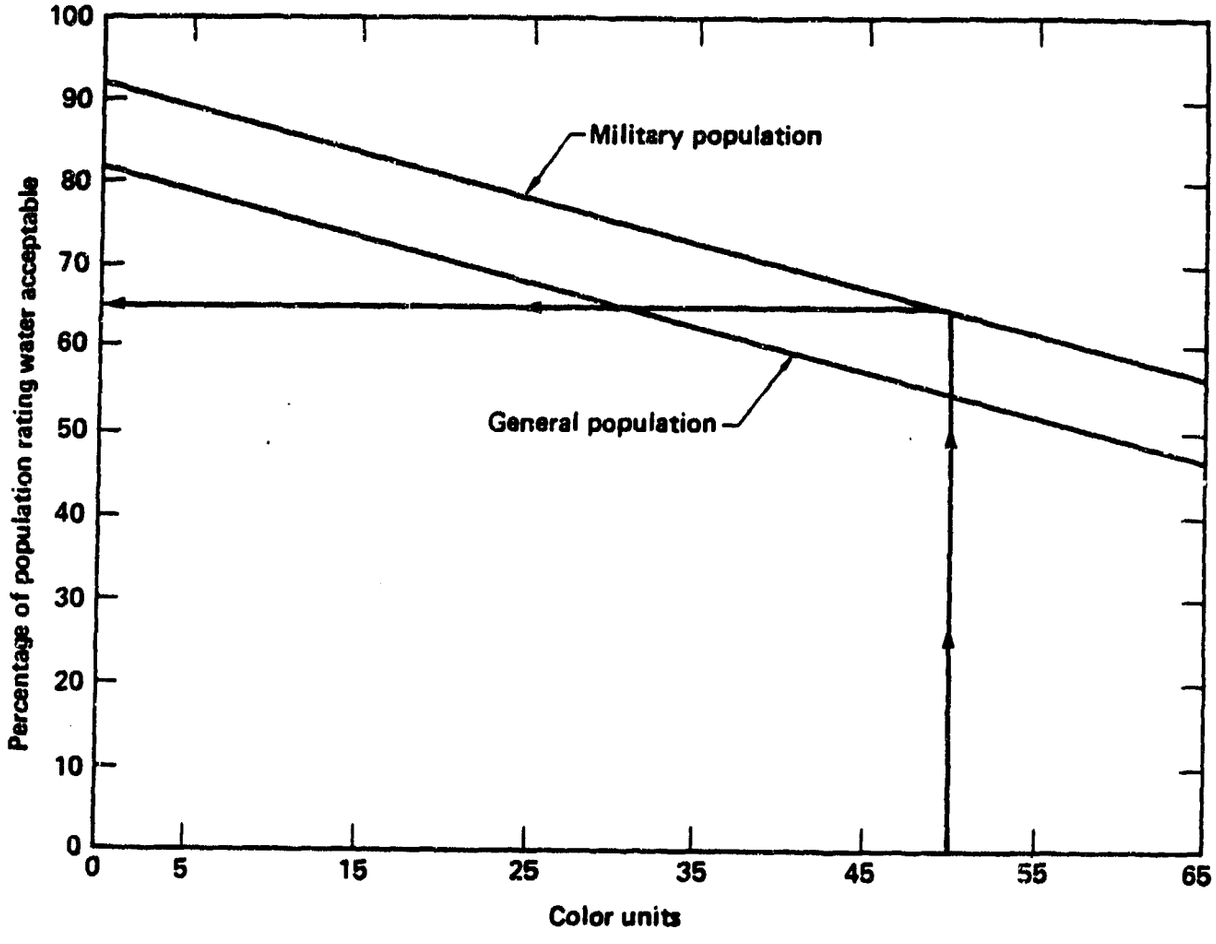

Figure 5. Comparison between military and general populations rating water acceptable based on color, when turbidity is fixed at 5 TU and threshold odor number is fixed at 3.

provoked to complain about the color level if it underwent rapid changes periodically than if it remained relatively high.[26] Although the difference in perception between 3 and 50 and between 3 and 15 color units probably is significant for most individuals, military personnel consuming field waters should not be regarded as having the same sensitivity to color as do civilian populations. More importantly, under the circumstances of mandatory water-consumption to support labor or combat in a hot, arid environment, and in the absence of any color-related health risks, water containing 15 and 50 color units for long and short periods of exposure, respectively, should be tolerable to military personnel--especially if they are properly trained.

RECOMMENDATIONS FOR COLOR STANDARDS

In summary, there is no evidence that a relationship exists between human health and the color in water. Color is accepted generally as an aesthetic standard, and it can be related to the population's acceptance of drinking water. Relative to acceptability, the military-acceptance curve indicates that a significant percentage of the population would reject the water at the present military color standard of 50 color units. Modification of the color standard to 15 color units significantly reduces the level of rejection. However, for short-term exposure periods ($\leq$ 7 d) we recommend a color level of 50 color units and for long-term exposure ($\leq$ 1 y) we recommend a color level of 15 color units because, in the absence of any water-related health risks, such color levels can be considered safe and tolerable.

ACKNOWLEDGMENTS

We thank Dr. William H. Bruvold, Professor of Public Health at the University of California, Berkeley, an authority on psychometric analysis of behavior associated with organoleptic parameters of water quality (e.g., taste, odor, color, and turbidity), for his critical review of this report. His constructive criticisms and suggestions represent important contributions to the data-base assessment.

APPENDIX A

TABULATION OF POPULATION ACCEPTABILITY PERCENTAGES

Table A-1 in this appendix is our tabulation of population-acceptability percentages for water for all combinations of turbidity, color, and odor values that were plotted by Harris in five charts.[1] Only 100 of the 125 combinations of turbidity, color, and odor were available in Harris's paper. The combinations for zero and 15 color units were grouped and analyzed together by Harris. For our calculations, we assigned the zero and 15 color-unit group a value of 10 color units. From these data we derived the following multiple-regression equation (the derivation of the equation is contained in Appendix B) for predicting the percent of the population that will rate water acceptable, given specific color, turbidity, and odor values.

$$A = 86 - 0.5(C) - 1(T) - 0.1(S), \qquad (A-1)$$

where

A = percentage of population rating water acceptable,
C = color units,
T = turbidity units, and
S = threshold odor number (TON).

Table A-1. General population acceptability percentages for water for all combinations of turbidity, color, and odor values.[a,b]

Color unit	Turbidity unit	Threshold odor number	Population acceptability (%)	Color unit	Turbidity unit	Threshold odor number	Population acceptability (%)
10	0	1	95	30	0	50	85
10	0	3	92	30	0	200	54
10	0	12	86	30	5	1	75
10	0	50	82	30	5	3	80
10	0	200	74	30	5	12	74
10	5	1	85	30	5	50	67
10	5	3	65	30	5	200	66
10	5	12	84	30	10	1	54
10	5	50	69	30	10	3	54
10	5	200	53	30	10	12	58
10	10	1	73	30	10	50	58
10	10	3	78	30	10	200	58
10	10	12	57	30	20	1	36
10	10	50	58	30	20	3	37
10	10	200	50	30	20	12	31
10	20	1	64	30	20	50	40
10	20	3	46	30	20	200	40
10	20	12	51	30	40	1	32
10	20	50	38	30	40	3	36
10	20	200	42	30	40	12	18
10	40	1	41	30	40	50	30
10	40	3	41	30	40	200	17
10	40	12	33	50	0	1	64
10	40	50	32	50	0	3	60
10	40	200	27	50	0	12	68
30	0	1	92	50	0	50	49
30	0	3	84	50	0	200	31
30	0	12	75	50	5	1	62

Table A-1. (Continued)

Color unit	Turbidity unit	Threshold odor number	Population acceptability (%)	Color unit	Turbidity unit	Threshold odor number	Population acceptability (%)
50	5	3	45	70	0	50	40
50	5	12	53	70	0	200	27
50	5	50	42	70	5	1	33
50	5	200	23	70	5	3	37
50	10	1	30	70	5	12	38
50	10	3	33	70	5	50	48
50	10	12	60	70	5	200	20
50	10	50	27	70	10	1	43
50	10	200	22	70	10	3	52
50	20	1	25	70	10	12	41
50	20	3	49	70	10	50	22
50	20	12	39	70	10	200	27
50	20	50	23	70	20	1	22
50	20	200	20	70	20	3	25
50	40	1	30	70	20	12	42
50	40	3	22	70	20	50	35
50	40	12	6	70	20	200	10
50	40	50	14	70	40	1	27
50	40	200	8	70	40	3	14
70	0	1	53	70	40	12	19
70	0	3	66	70	40	50	13
70	0	12	53	70	40	200	10

[a] Tabulated from Harris's data.[1]

[b] The zero and 15 color-value groups in Harris's[1] data were combined for our calculations into one group with a value of 10 color units.

APPENDIX B

DERIVATION OF MULTIPLE-REGRESSION EQUATION FOR COMPUTING POPULATION ACCEPTABILITY PERCENTAGE FOR ALL COMBINATIONS OF TURBIDITY, COLOR, AND ODOR IN DRINKING WATER

A multiple-regression equation of the form

$$y = b_0 + b_1x_1 + b_2x_2 + \ldots + b_kx_k \qquad \text{(B-1)}$$

was fit to the data shown in Table A-1 (Appendix A) to describe the joint relationship of population-acceptability percentage to turbidity, color, and odor in drinking water. The coefficients b_k in Eq. B-1 are calculated to furnish the minimum sum of squares of differences between the dependent y variable and the linear combination of x variables. The solution for the coefficients was obtained using the following set of mathematical expressions:

$$\Sigma(X_{1,i}Y_i) = b_1\Sigma(X_{1,i})^2 + b_2\Sigma(X_{1,i}X_{2,i}) + b_3\Sigma(X_{1,i}X_{3,i}); \qquad \text{(B-2a)}$$

$$\Sigma(X_{2,i}Y_i) = b_1\Sigma(X_{1,i}X_{2,i}) + b_2\Sigma(X_{2,i})^2 + b_3\Sigma(X_{2,i}X_{3,i}); \text{ and} \qquad \text{(B-2b)}$$

$$\Sigma(X_{3,i}Y_i) = b_1\Sigma(X_{1,i}X_{3,i}) + b_2\Sigma(X_{2,i}X_{3,i}) + b_3\Sigma(X_{3,i})^2; \qquad \text{(B-2c)}$$

where

- $X_{n,i}$ = $(\bar{x}_{n,i} - \bar{x}_n)$ where $\bar{x}_n$ is the arithmetic mean for all 100 $\bar{x}_{n,i}$ values, and n = either 1, 2, or 3;
- i = integer between 1 and 100;
- Y_i = $(\bar{y}_i - \bar{y})$, and $\bar{y}$ is the arithmetic mean for all 100 $\bar{y}_i$ values; and
- y_i = population acceptability (%);
- $x_{1,i}$ = color-unit value;
- $x_{2,i}$ = turbidity-unit value; and
- $x_{3,i}$ = threshold odor number (TON) value

as derived from Harris's data[1] in Table A-1 (Appendix A).

The calculations used to solve Eqs. B-2a, B-2b, and B-2c are as follows:

$\sum(X_{1,i}Y_i) = \sum(x_{1,i} - x_1)(y_i - y) = -25{,}440;$

$\sum(X_{2,i}Y_i) = \sum(x_{2,i} - x_2)(y_i - y) = -20{,}590;$

$\sum(X_{3,i}Y_i) = \sum(x_{3,i} - x_3)(y_i - y) = -48{,}869;$

$\sum(X_{1,i})^2 = \sum(x_{1,i} - x_1)^2 = 50{,}000;$

$\sum(X_{2,i})^2 = \sum(x_{2,i} - x_2)^2 = 20{,}000;$

$\sum(X_{3,i})^2 = \sum(x_{3,i} - x_3)^2 = 570{,}056;$

$\sum(X_{1,i}X_{2,i}) = \sum(x_{1,i} - x_1)(x_{2,i} - x_2) = 0;$

$\sum(X_{1,i}X_{3,i}) = \sum(x_{1,i} - x_1)(x_{3,i} - x_3) = 0;$ and

$\sum(X_{2,i}X_{3,i}) = \sum(x_{2,i} - x_2)(x_{3,i} - x_3) = 0.$

Therefore, the three equations used to determine the coefficients b_1, b_2, and b_3 are

$$-25{,}440 = b_1(50{,}000) + b_2(0) + b_3(0), \qquad \text{(B-2a)}$$

$$-20{,}590 = b_1(0) + b_2(20{,}000) + b_3(0), \text{ and} \qquad \text{(B-2b)}$$

$$-48{,}869 = b_1(0) + b_2(0) + b_3(570{,}056). \qquad \text{(B-2c)}$$

The solutions to equations B-2a, B-2b, and B-2c yield, respectively:

$b_1 = -0.5088$,

$b_2 = -1.0295$, and

$b_3 = -0.0857$.

Now, we substitute the above values for b_1, b_2, and b_3 and the values for y and x_1, x_2, and x_3 into the regression formula:

$$y = b_0 + b_1x_1 + b_2x_2 + b_3x_3 , \qquad \text{(B-3)}$$

where

$$y = \frac{\sum y_i}{100} = 45.89;$$

$$x_1 = \frac{\sum x_{1,i}}{100} = 40;$$

$$x_2 = \frac{\sum x_{2,i}}{100} = 15; \text{ and}$$

$$x_3 = \frac{\sum x_{3,i}}{100} = 53.2,$$

and solve for b_0:

$b_0 = 86.24$.

Consequently, the multiple-regression equation for determining the population-acceptability percentage (y) for drinking water containing any combination of color (x_1), turbidity (x_2), or odor (x_3) can be expressed as

$y = 86 - 0.5\ (x_1) - 1\ (x_2) - 0.1\ (x_3)$, or equivalently, (B-4)

$A = 86 - 0.5(C) - 1(T) - 0.1(S)$, which is Eq. A-1 in Appendix A.

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CHAPTER 3. TOTAL DISSOLVED SOLIDS

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ABSTRACT

The principal objective of this chapter is to recommend drinking-water standards for total dissolved solids (TDS) in military field-water supplies. In support of this goal we describe the typical properties and concentrations of TDS in natural waters, and we review the evidence for potential health consequences for troops exposed to water containing high concentrations of TDS.

After assessing health-effects literature, we concluded that high TDS concentrations are not clearly linked with specific health effects; however, high TDS concentrations in water will make the taste of the water objectionable to many individuals, causing them to reject it. In some situations, these individuals could become susceptible to dehydration, which could lead to performance-degrading effects.

We use a methodology from the literature to estimate the proportion of field personnel that would refuse to drink water based on its TDS content. We then develop recommendations for TDS standards for military field-water supplies based on this computational procedure. According to our calculations, consideration should be given to lowering the present military field-water-quality standard for TDS from 1500 mg/L to 1000 mg/L. This reduction would reduce the percentage of the military population that might refuse to drink the water from approximately 7% for a 1500-mg/L TDS standard to about 2% for the 1000-mg/L TDS standard. Additionally, the 2% figure probably could be lowered even more if proper water-consumption discipline were enforced. A 1000-mg/L TDS standard should also reduce the incidence of laxative effects from elevated TDS among the military population consuming the water and possibly accelerate the adaptation process for those individuals accustomed to the taste of water with lower TDS.

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INTRODUCTION

The total dissolved solids (TDS) content of water affects its taste and therefore its acceptability for consumption. In the first part of this chapter, we describe concentrations of TDS in natural waters, methods of measuring TDS, and potential health effects related to TDS. We then discuss a procedure for calculating drinking-water standards for TDS in military field water. Using the procedure just mentioned, we derive recommendations for TDS standards and discuss the uncertainties associated with our recommendations.

GENERAL PROPERTIES

Mineral salts and small amounts of other inorganic and organic substances constitute the filterable residue content of water (i.e., the material that will pass through a standard glass-fiber filter disk). The concentration of filterable residue is commonly expressed as milligrams per liter (mg/L) of TDS.[1,2] Typically, the ions of the mineral salts are the predominant constituents of the dissolved material; consequently, TDS generally refers to salinity.[3] The principal cations constituting TDS are calcium (Ca^{+2}), magnesium (Mg^{+2}), potassium (K^{+}), and sodium (Na^{+}); the chief anions are bicarbonate (HCO_3^{-}), carbonate (CO_3^{-2}), chloride (Cl^{-}), sulfate (SO_4^{-2}), and in ground waters, nitrate (NO_3^{-}).[1]

The dissolved substances that constitute TDS are encountered in all natural waters, and they enter the water from natural as well as anthropogenic processes. Although TDS are ubiquitous in nature, neither the TDS content nor the ratio of the TDS concentration to the concentration of each individual ion constituting TDS is constant for all water. The relative proportions of TDS constituents in natural waters are a function of geochemical processes (e.g., weathering) acting on local geological strata.[4] In fact, this relationship between local geology and the chemical constituents of natural waters explains why frequently only the TDS concentration is used as a convenient basis for dividing natural waters into four general categories: fresh, brackish, saline, or brine. Table 1 shows the separation of natural waters into the four general categories and the TDS concentration that corresponds to each category.

The TDS concentration of drinking water commonly ranges from levels below 500 mg/L to amounts exceeding 2000 mg/L. Seawater is considered to be the typical worst-case challenge for military water-purification equipment because of its high TDS concentration (~35,000 mg/L), and because it is an important source of water for desalination equipment used to support military operations.

Table 1. General categories of natural waters based on TDS concentration.[3]

Category	TDS (mg/L)
Fresh water	<1000
Brackish water	1000 to ≥ 20,000
Saline water	≥35,000
Brine	>>35,000 (e.g., 100,000)

APPLICABLE DETECTION METHODS

The concentration of TDS in natural waters can be measured directly or estimated from measurements of individual constituents. One method for estimating TDS involves measuring alkalinity (CO_3^{-2}, HCO_3^-, OH^-), sulfate (SO_4^{-2}), and chloride (Cl^-) concentrations, using standard U.S. Army procedures, and then inserting these measurements into the following equation.[5]

$$TDS = A + 1.4\,S + 1.6\,C \quad , \tag{1}$$

where

TDS = total dissolved solids, mg/L;
A = alkalinity, mg/L;
S = sulfate concentration, mg/L;
C = chloride concentration, mg/L.

The TDS concentration can also be estimated faster and more conveniently by measuring the electrical conductivity of a water sample, using a conductivity meter.[3] The TDS concentration is then approximated by multiplying the measured electrical conductivity by an appropriate conversion factor related to the expected ionic composition and the temperature of the measured water. For most natural waters, the conversion factor ranges from 0.55 to 0.90.[2] This technique is available to U.S. Army personnel.[6] One other method involves weighing the total filterable residue that remains after evaporation of a known quantity of water and drying to a constant weight at 180°C.[2,4]

HEALTH EFFECTS

Ingestion of water containing a high TDS concentration may produce an osmotic pressure in the intestinal tract that is high enough to prevent absorption of water through the intestinal wall; the large volume of fluid retained in the intestine increases the motility of the smooth muscle lining the intestinal wall, and this increased contractile activity helps to flush the large intestine, thereby producing a laxative effect.[7,8]

An additional explanation for the laxative effects of elevated TDS levels is the action of specific ions.[9] For example, research shows that dramatic increases in laxative effects for TDS levels exceeding 1000 mg/L[1,10,11] may actually have resulted from uncontrolled confounding factors such as the effects of Mg^{+2} and SO_4^{-2}, or to biological contamination, and not necessarily from the collective effect of all constituents of TDS.

The primary problem with a high TDS concentration is its effect on taste. As the TDS content of a water increases, its taste becomes increasingly worse.[12,13] One consequence of bad water taste is decreased consumption.[14] In some situations, where large volumes of water must be consumed to replace sweat losses, decreased consumption caused by poor water taste could make some individuals susceptible to dehydration. The actual debilitating effects of dehydration, described by Adolph et al.,[15] progress in the following sequence.

- Discomfort
- Weariness
- Muscle weakness
- Apathy
- Impaired coordination
- Delirium
- Heat stroke

Additionally, Walker et al.[16] state that intense thirst is experienced over the first 2 d of water deprivation; weakness and confusion occur during the 3rd day of abstention; and death results within approximately 10 d when 15% of the body weight is lost in sweat and respiration. In this context military field water should have levels of dissolved solids that are not likely to cause rejection; otherwise, dehydration and heat prostration may occur.

We conclude that TDS is a useful water-quality measurement for two important reasons. First, it is an indicator of the taste of water, and poor water taste is a basis for refusal to drink water. Consequently, the debilitating effects of dehydration may

follow. Second, the measurement of TDS is essential for monitoring the effectiveness of water-purification equipment (e.g., a reverse osmosis water purification unit) designed to desalinate high TDS waters so that such waters can be consumed by military personnel.

DEVELOPMENT OF RECOMMENDATIONS FOR STANDARDS

The United States Public Health Service (USPHS) has recommended a TDS standard of 500 mg/L.[10] This TDS concentration has also been established as a reasonable goal for drinking-water quality by the U.S. Environmental Protection Agency (U.S. EPA).[13] According to Bruvold[17] and Bruvold and Ongerth,[12] no scientific justification exists for the TDS standard set by the USPHS. Consequently, no scientific basis is apparent for the reasonable goal for TDS established by the U.S. EPA. For example, many public drinking-water supplies in the United States have TDS concentrations exceeding 2000 mg/L, and, apparently, an acclimated population can tolerate this concentration without any ill effects.[10,12,13] In fact, no evidence exists that unacclimated individuals ever reported health consequences voluntarily to public health authorities after consuming such waters. Moreover, the current U.S. Army standard for TDS is 1500 mg/L,[18] and this standard cannot be substantiated scientifically. Therefore, a more quantitative approach is needed for developing recommendations for TDS standards for the U.S. Army, as well as for civilian populations.

The procedure we adopted for this purpose employs the technique and data of Bruvold and Ongerth.[12] This technique defines a quantitative relationship between the mineral content of water (TDS), the general taste quality of water, and the intention of an individual to drink the water. By this method, the proportion of a population rejecting water (and hence susceptible to dehydration) as a consequence of the TDS concentration can be estimated and standards can be developed accordingly.

METHODOLOGY

The Bruvold and Ongerth[12] approach was based on the use of taste panels to assess the general taste quality of natural waters by psychometric scaling methods. Two psychometric rating scales, a quality scale (Q) and an action-tendency (AT) scale, were an integral part of this approach. An explanation of the derivation and application of these scales follows.

Derivation of Q and AT Psychometric Rating Scales

The Q and AT rating scales and scale values used by Bruvold and Ongerth[12] were developed by Bruvold[19] in an earlier study. Bruvold constructed them according to the method of equal-appearing intervals described by Edwards.[20] Accordingly, 53 adult subjects were instructed to place each of 34 Q and then 18 AT statements into one of 11 numerically identified categories. The 34 Q statements described the taste of water (e.g., "This water has an excellent taste"), and the 18 AT statements referred to the behavioral response of the individual concerning actual consumption of the water (e.g., "I could never drink this water"). The 11 categories into which the statements were to be placed represented an 11-interval psychological continuum describing degrees of unfavorableness or favorableness for each subject. For example, the subjects were told that degrees of unfavorableness decrease from the 1st to the 5th category; the 6th category is considered neutral, and the degrees of favorableness increase from the 7th to the 11th category. The judgments of three subjects were rejected because these subjects did not divide the statements into the 11 categories in the prescribed manner.[19]

Once all of the subjects separated the 34 Q statements and then the 18 AT statements into each of the 11 categories, and the judgments of the three previously mentioned subjects were discarded, scale values were derived for each of the statements. The median of the distribution of the 50 judgments obtained for each statement on the 11-interval psychological continuum was used as the scale value for that statement. The median or scale value for each statement was determined from a mathematical equation or directly from a graph of the relationship between the cumulative proportions of judgments and the 11-interval psychological continuum into which the statement was distributed by each of the 50 subjects.[20]

To construct Q and AT rating scales with equal-appearing intervals between scale values, and thereby to reduce the number of statements, the interquartile range was determined first for each statement. This value represented the spread or variation of the middle 50% of the judgments (i.e., the number of intervals between the 25th and 75th percentiles) for a particular statement on the 11-interval continuum. A large interquartile range measurement meant a statement was ambiguous and should be removed from the scale. Additionally, the interquartile range value was used for choosing between two or more statements with equal scale values but unequal interquartile ranges. The interquartile range value for each statement was determined mathematically or graphically in ways similar to those used for determining scale values.[20] In summary, Bruvold[19] used both scale and interquartile range values as the criteria for constructing

the Q and AT psychometric rating scales from the original 34 Q and 18 AT statements. The resulting scales were thereby reduced to nine statements with nearly equal distances between scale values and a relatively small interquartile range associated with each statement.[19]

Application of Q and AT Psychometric Rating Scales

The Q and AT rating scales, which were constructed by Bruvold,[19] were applied by Bruvold and Ongerth[12] using the following procedure. A taste panel of 20 adults (13 male and 7 female) was asked to use the two psychometric rating scales to evaluate the taste of 29 different natural waters from California. These natural waters contained TDS concentrations ranging from about 50 to 2200 mg/L, levels that represent a typical range for TDS concentration in natural waters. Water samples were presented at room temperature to the taste panelist. According to results from earlier research, sample temperatures between 40°F and 72°F had minimal systematic effect on ratings[12]. The Q scale consisted of the nine Q statements shown in Table 2, which describe the taste of water in qualitative terms. The AT scale contained the nine AT statements shown in Table 3, which refer to the behavioral response of the individual concerning the actual consumption of the water. The 20 taste-panel members were instructed to score natural water samples on both Q and AT rating scales using the scale values associated with each statement that best described their judgment. The mean Q and AT scores were then calculated for each natural water sample from the 20 scores that were recorded.

To evaluate the relationship between the mean Q and AT scores and the TDS concentration corresponding to these mean scores, Bruvold and Ongerth[12] plotted the data and used linear regression analysis to calculate the lines of best fit through each set of data points. This analysis revealed that an inverse linear relationship exists between taste-quality scores and TDS concentration and between behavioral intention scores and TDS concentration. By assuming a normal distribution around each line of best fit and a constant standard error of estimation for each scale, Bruvold and Ongerth[12] showed that the regression equations and the corresponding standard errors of estimation, in combination with z-score equations, could be used to estimate the proportion of people rating water at or below a certain value on the Q or AT rating scale. Thus, this procedure could be used to estimate the percentage of a population that would rate a water unacceptable on the basis of taste and, consequently, TDS content. Therefore, the TDS standards recommended for military field-water supplies could be expressed quantitatively in terms of the acceptable proportion of troops that would rate the water at a specific level of unacceptability on the Q or AT rating scale.

Table 2. Quality (Q) scale for describing the taste of water.[12]

Statement	Median scale value
This water has an excellent taste.	10.67
This water has a very good taste.	9.79
This water has a good taste.	8.45
This water has a slightly good taste.	7.16
This water has a neutral taste.	6.00
This water has a slightly bad taste.	4.61
Boundary scale value for military unacceptability	3.78[a]
This water has a bad taste.	2.95
This water has a very bad taste	2.05
This water has a horrible taste.	1.16

[a] Scale value representing the point where it is assumed that military personnel would refuse to drink the water.

ACCEPTABILITY OF MILITARY FIELD-WATER SUPPLIES BASED ON TDS CONCENTRATION

Actual calculation of the TDS standards for military field-water supplies, using the Bruvold and Ongerth[12] procedure, requires the following assumptions. First, the TDS content of the 29 different natural waters used in the taste survey is assumed to represent the range of TDS concentrations found in the natural or purified waters that are encountered typically by military personnel. Second, the taste panel of 20 adults is assumed to have the same taste response as military personnel. Third, ratings of the general taste quality of water at or below 3.78 on the Q scale (the boundary scale value for delineating the statement that, "This water has a bad taste")* and at or below 3.43 on the AT scale (the boundary scale value for delineating the statement that, "I could not accept this water as my everyday drinking water") are assumed to be the critical scale

* Boundary scale values are used because the Q and AT scales are presumed to be continuous. Therefore, the separation between adjacent statement categories is assumed to be at the arithmetic mean scale value between the two statements and not at the median scale value for either statement.

Table 3. Action-tendency (AT) scale for describing a behavioral response to the taste of water.[12]

Statement	Median scale value
I would be very happy to accept this water as my everyday drinking water	9.96
I would be happy to accept this water as my everyday drinking water	9.20
I am sure that I could accept this water as my everyday drinking water	8.07
I could accept this water as my everyday drinking water.	7.35
Maybe I could accept this water as my everyday drinking water.	5.64
I don't think I could accept this water as my everyday drinking water.	4.21
Boundary scale value for military unacceptability	3.43[a]
I could not accept this water as my everyday drinking water.	2.65
I could never drink this water.	1.27
I can't stand this water in my mouth and I could never drink it.	1.05

[a] Scale value that represents the point where it is assumed that military personnel would refuse to drink the water.

values. These values indicate the point where military personnel would be so dissatisfied with a water supply that they would refuse to drink it or would substantially reduce their water consumption, thereby becoming susceptible to dehydration (see Tables 2 and 3). Finally, a normal distribution is assumed to exist around the lines best fitting the relationship between TDS concentrations and Q and AT values derived by Bruvold and Ongerth,[12] and a constant standard error of estimation is assumed for each scale.

The relationship between TDS concentration and the percentage of the population rating water at or below a particular Q or AT scale rating can now be expressed mathematically using the regression equations and standard errors of estimation in combination with z-score equations. For example, the mean Q or AT rating can be estimated for any water supply by measuring the TDS concentration and then inserting that value into the applicable regression equation:

$$\mu_Q = 7.60 - 0.00213\ [TDS]\ , \tag{2}$$

$$\mu_{AT} = 8.03 - 0.00163\ [TDS]\ , \tag{3}$$

where

μ_Q = mean Q-scale rating;
[TDS] = concentration of total dissolved solids in the water supply; and
μ_{AT} = mean AT-scale rating.

The standard error of estimation for the mean Q-scale rating (σ_Q) is 1.47; the standard error of estimation for the mean AT-scale rating (σ_{AT}) is 1.46. According to these equations, the mean Q- and AT-scale ratings for a water supply containing a TDS concentration of 500 mg/L would be 6.54 and 7.22, respectively. The mean Q-scale rating (μ_Q) of 6.54 indicates that 50% of the population would indicate that the "water has a neutral taste" or worse, and 50% would indicate that the "water has a slightly good taste" or better (see Table 2). The mean AT-scale rating (μ_{AT}) of 7.22 indicates that 50% of the population would rate the water acceptable for everyday consumption or better and 50% would rate the water as "maybe" they could accept it for everyday consumption or worse (see Table 3). The mean Q-scale rating value and the mean AT-scale rating value indicate the median response for a population because the regression equations describe the lines of best fit for the data from the taste-panel study; as stated previously, a normal distribution is assumed to exist around the lines of best fit.

The mean Q or AT value (μ) can then be incorporated into a z-score equation, along with the respective standard error of estimation (σ) for the Q or AT scale, and the respective scale value that represents the point on either scale at or below which it is assumed that military personnel might refuse to drink the water (i.e., Q = 3.78 and AT = 3.43). Thus, the solution to the z-score equation is a standard normal deviate that corresponds to the proportion of the population on each scale that would refuse to drink the water based on its taste.

For example, the z-score equation is expressed as

$$z_{\%} = \frac{x - \mu}{\sigma} , \qquad (4)$$

where

$z_{\%}$ = standard normal deviate corresponding to a percentage of the population;
x = Q or AT rating corresponding to the scale value at or below which a certain percentage of military personnel will score the water supply after tasting it (e.g., x_Q = 3.78 and x_{AT} = 3.43 for the case where military personnel will refuse to drink the water);
μ = mean Q- or AT-scale rating calculated from Eqs. 2 or 3, respectively; and

σ = standard error of estimation for Q- or AT-rating scale (i.e., $\sigma_Q = 1.47$ and $\sigma_{AT} = 1.46$).

For a water supply containing a TDS concentration of 500 mg/L, the standard normal deviates for the situation where military personnel will refuse to drink the water are calculated to be -1.88 and -2.60 for the Q and AT scales, respectively. The percentage of the population corresponding to each standard normal deviate is determined from a table of values for the standard normal distribution.[21] Based on the standard normal deviate calculated from the mean Q value corresponding to a TDS concentration of 500 mg/L, the percentage of the population that will complain about the bad taste of the water and refuse to drink it ($x_Q = 3.78$) is estimated to be about 3%. Based on the standard normal deviate calculated from the mean AT rating value corresponding to a TDS concentration of 500 mg/L, the percentage of the population that could not accept the water because of its poor taste ($x_{AT} = 3.43$) is estimated to be approximately 0.5%.

The z-score equation can also be used to estimate the Q or AT value at or below which a specified proportion of the population will rate a water. According to this application of the z-score equation, when the water supply contains 500 mg/L of TDS and the rating score for 10% of the population is of interest, then $z_{\%} = -1.28$ and x equals 4.66 for the Q value and x equals 5.35 for the AT value (see Tables 2 and 3 for closest corresponding statements).

Calculations similar to those discussed previously were used to construct the graphs in Figs. 1 and 2. Figures 1 and 2 show the relationship between TDS concentration and the percentage of the military population rating water unacceptable on the Q (≤ 3.78) and AT (≤ 3.43) rating scales, respectively, and therefore at risk of refusing to drink the water because of an objectionable taste produced by the TDS concentration. Both Figs. 1 and 2 could be used to calculate TDS standards, once a percentage of military personnel at risk of dehydration has been defined. However, the fact that the slopes of the AT lines in Fig. 2 are not as steep as the slopes of the Q lines in Fig. 1 suggests that people may actually accept water that has a poor taste, as Bruvold and Ongerth[12] indicated in their paper. This means that the AT scale is the appropriate one to use for determining TDS standards, although military personnel may complain about the taste of water even if they do drink it. Thus, the AT lines in Figure 2 are best suited for estimating the proportion of the military population that would refuse to drink the water and thereby become susceptible to dehydration.

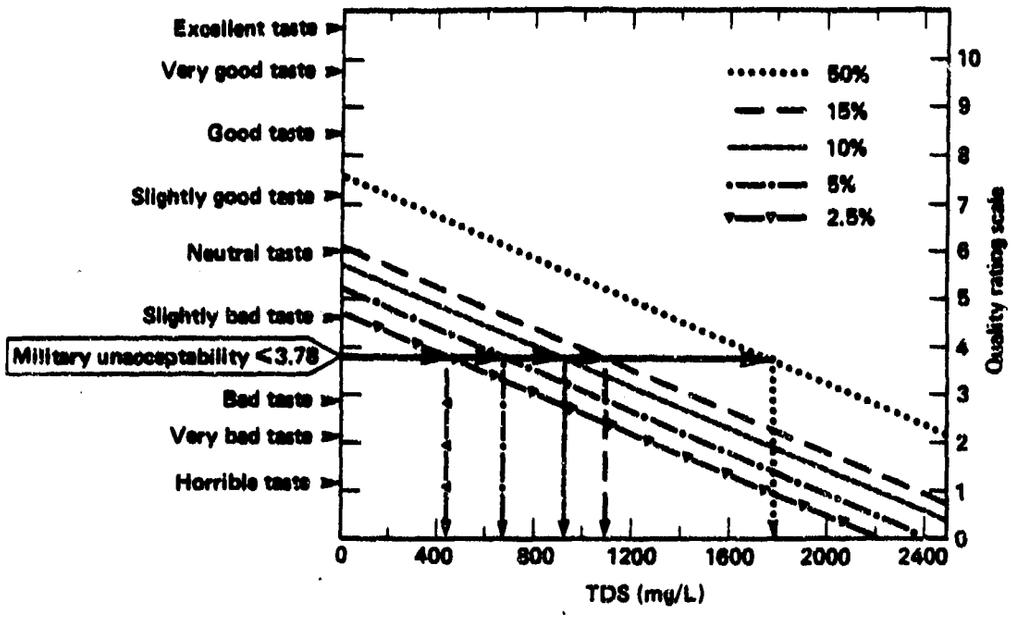

Figure 1. Relationship between TDS concentration and percentage of military population rating water unacceptable on the quality (Q) rating scale (i.e., ≤ 3.78, the boundary scale value for defining military unacceptability). Extrapolated from analyses by Bruvold and Ongerth[12] of taste-panel responses to California water supplies.

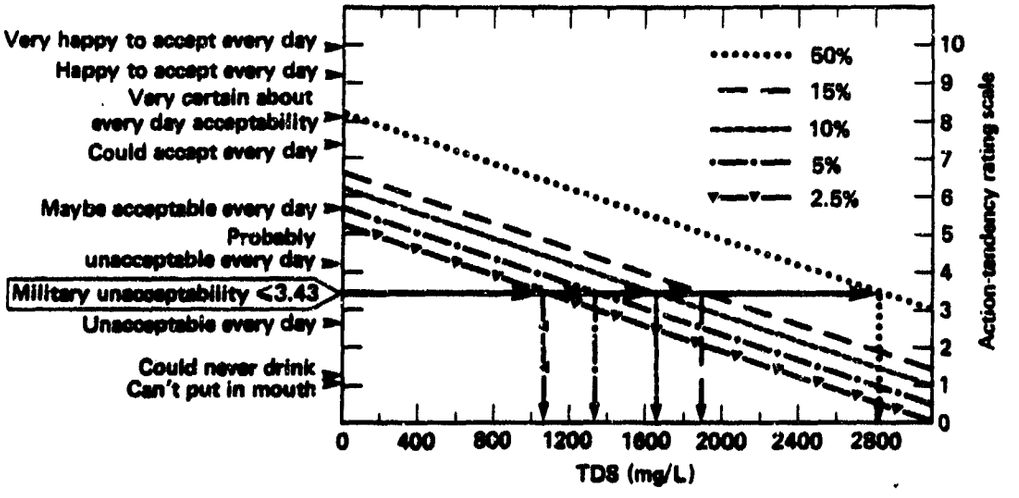

Figure 2. Relationship between TDS concentration and percentage of military population rating water unacceptable on the action-tendency (AT) scale (i.e., ≤ 3.43, the boundary scale value defining military unacceptability). Extrapolated from analyses by Bruvold and Ongerth[12] of taste-panel responses to California water supplies.

RECOMMENDATIONS FOR STANDARDS

Table 4 displays a comparison between three TDS concentrations and the corresponding percentages of military personnel that would refuse to drink the water ($AT \leq 3.43$) or complain of bad taste ($Q \leq 3.78$). These three TDS concentrations represent possible standards for the TDS content of military field water. At the current U.S. Army field-water standard for TDS, which is 1500 mg/L, 6.9% of the military population would consider the water unacceptable for consumption, although an estimated 34% of the military population would complain that the water had a bad taste. Increasing the TDS standard to 1800 mg/L means that the proportion of the military population that would refuse to drink the water would increase to 13%, and approximately half of the exposed military population would complain about the objectionable taste of such water. However, if the TDS standard were reduced to 1000 mg/L, then only about 2% of the exposed military population would be at risk of dehydration. Lowering the TDS standard to 1000 mg/L would also reduce complaints about taste to an estimated 12% of the exposed military population. Of course, achieving TDS concentrations less than 1000 mg/L would facilitate consumption of adequate amounts of water by military personnel, particularly when military operations are conducted in arid regions.

A TDS standard of 1000 mg/L might serve two additional functions. First, this standard should minimize the likelihood of any dramatic increase in laxative effects among the military population actually consuming the water. This is consistent with evidence in the literature,[1,11] particularly in a paper by Moore,[11] which suggests that consumption of water with TDS levels exceeding 1000 mg/L might be directly responsible for increased laxative effects. Second, those military personnel accustomed to drinking from U.S. drinking-water supplies that serve major cities might be able to adapt more quickly to a TDS level of 1000 mg/L rather than 1500 mg/L. This is because the majority of U.S. drinking-water supplies serving major cities typically contain TDS levels of only 500 mg/L or less.[22] According to the previous comparison, decreasing the present TDS standard from 1500 mg/L to 1000 mg/L would reduce the percentage of troops at risk of dehydration and would lower substantially the number of complaints about the taste of the water. Furthermore, at a TDS standard of 1000 mg/L, the estimated percentage of troops refusing to drink the water because of poor palatability is only about 2%, and it is not unreasonable to assume that this percentage could be reduced significantly by strict enforcement of a suitable water-consumption discipline. However, substantially lowering the proportion of troops at risk of dehydration from levels at or above 5% probably could not be accomplished easily by water-consumption discipline because the corresponding large proportion of the population ($\geq 26\%$) complaining about the bad taste would become a

Table 4. Comparison between TDS concentrations considered as possible standards for military field-water supplies, and corresponding proportions of military population refusing to drink the water or complaining that it has a bad taste.

Possible standard for TDS in field water (mg/L)	Proportion of military population (%)	
	Refusing to drink water	Complaining about taste of water
1000	2.1	12
1500[a]	6.9	34
1800	13	50

[a] Current standard for TDS applied to military field-water supplies.[16]

factor. Therefore, the data indicate that consideration should be given to changing the present TDS standard of 1500 mg/L to 1000 mg/L unless the U.S. Army is willing to accept more than 5% of the troops at risk of dehydration and more than one third of the troops complaining about bad taste. The possibility also exists that a dramatic increase in laxative effects could occur among those unacclimated troops actually consuming water containing more than 1000 mg/L of TDS. Our recommendation for changing the TDS standard remains applicable to both short-term (7-d) and long-term (1-y) exposure periods because the primary direct effects of TDS concentration are instantaneous behavioral responses based on taste, and this relationship remains constant for all periods of exposure.

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CHAPTER 4. CHLORIDE

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ABSTRACT

The purpose of this chapter is to recommend drinking-water standards for the chloride anion (Cl^-) in military field-water supplies. In support of this goal we describe the typical properties and concentrations of chloride in natural waters, and we review the evidence for human health consequences for military personnel exposed to water with a high chloride content.

The relationship between health effects and chloride concentrations in drinking-water supplies is poorly documented. However, the available evidence suggests that chloride will give water an objectionable taste for many individuals at concentrations well below those that cause laxative effects. Consequently, individuals that refuse to drink such poor-tasting water are susceptible to dehydration in situations where large sweat losses must be replaced by increased water intake.

Because chloride is a constituent of the total dissolved solids (TDS) content of water (particularly field water that has been processed through a reverse osmosis water-purification unit (ROWPU)), and because both TDS and chloride cause an objectionable taste, we convert the chloride concentration to a TDS content for the water. Then, we estimate quantitatively the proportion of the military population that will refuse to drink water, based on the TDS concentration. Using this computational procedure, we then recommend chloride standards for military field-water supplies. According to our calculations, the present field-water-quality standard for chloride, 600 mg/L for both short-term (7-d) and long-term (1-y) exposure periods, could be retained because we estimate that only about 2% of the military population will refuse to drink such water.

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INTRODUCTION

Chloride occurs in natural waters in the form of the chloride anion (Cl^-). The importance of the chloride anion as a water-quality parameter for military field-water supplies is related to evidence that elevated concentrations of chloride can cause the taste of water to be objectionable, especially in combination with sodium cations, and may even induce laxative effects upon ingestion. In this chapter we describe the general properties of chloride in water, the concentrations of chloride that may be encountered in natural waters, and methods of detection. We also review the potential health effects of chloride as well as its taste properties. We then derive recommendations for standards for chloride in field-water supplies. Finally, we identify the additional research appropriate for resolving the principal uncertainties related to our recommendations.

GENERAL PROPERTIES

The chloride anion is a constituent of virtually all natural waters, and it contributes to the total dissolved solids (TDS) content of these waters.[1-3] Typically, brine and seawater contain high TDS concentrations that are composed primarily of chloride anions (~55% of TDS by weight) and sodium cations (~30% of TDS by weight). In comparison, the TDS concentration in fresh water is much lower and the chloride anion constitutes a smaller proportion of this TDS concentration (~10% or less of TDS by weight). Other anions such as sulfate and bicarbonate are the predominant anionic constituents of TDS in fresh water. Examples of chloride concentrations measured in natural waters are shown in Table 1.

Sources of the chloride anion in natural waters include (1) drainage from mineral deposits; (2) seawater intrusion or the deposition of sea spray following transport by wind and rain; (3) sewage contamination; (4) runoff from fields containing salts that were introduced by agricultural practices; and (5) effluent from industrial projects such as oil wells, petroleum refineries, galvanizing plants, water-softening facilities, and paper works.[3,9] Evaporite deposits (sedimentary rocks resulting from the evaporation of seawater in an enclosed basin), including halite (NaCl), sylvite (KCl), bischofite ($MgCl_2 \cdot 6H_2O$), and carnallite ($KMgCl_3 \cdot 6H_2O$), are the predominant sources of chloride for fresh waters, primarily because these salts are extremely soluble in water.[1]

The concentration of Cl^- in drinking waters can vary over a wide range (see Table 1). For example, in the southwestern United States, particularly Arizona, the chloride-ion concentration of drinking water has been reported to range from 6 to 1500 mg/L.[6]

Table 1. Chloride concentrations in natural waters.

Water source	Cl^- conc. (mg/L)	Reference
Dead Sea, Israel	280,000	4
Brine (292-ft well) in New Mexico	189,000	1
Great Salt Lake, Utah	143,500	5
Seawater[a]	19,400 (~55% by wt of TDS)	5
Rhine River:		5
Leaving Swiss Alps	1.1	
Germany/Holland border	178	
U.S. drinking-water supplies:		
Arizona	6 to 1500	6
Galveston, Texas	422	7
Spring and wells in Hawaii	950 to 1100	8

[a] Seawater is the typical worst-case chloride challenge for military water-purification equipment because of the large supply of ocean water available for desalination.

APPLICABLE DETECTION METHODS

Currently, the U.S. Army determines the concentration of chloride in water by using potassium chromate to indicate the end point of silver nitrate titration of chloride.[10] The chloride concentration is equated mathematically with the amount of silver nitrate required to change the water color from a yellowish shade to a reddish one. This technique is known as the argentometric method and is described in detail in the 15th edition of Standard Methods for the Examination of Water and Wastewater.[11] The potentiometric method, which employs a pair of electrodes and a voltmeter to detect the end point of titration of chloride by silver nitrate, is recommended for chloride by the U.S. Environmental Protection Agency[12] for compliance with National Secondary Drinking Water Standards. These methods are accurate and precise enough to detect chloride concentrations below 10 mg/L in the majority of natural waters.[11]

More automated analytical equipment for measuring chloride concentration in field waters may become available in the future for field use by the U.S. Army. For example, the automated ferricyanide method tentatively recommended for chloride detection in Standard Methods[11] may eventually become compatible with military field requirements for accurate, precise, rugged, reliable, and miniaturized equipment. Alternatively, an

ion-specific electrode may be developed that would be suitable for military field application. Such automated, rugged, reliable, and miniaturized equipment will improve the military's field capability to detect quickly, accurately, precisely, and efficiently the chloride concentration in field waters.

PHARMACOKINETICS

The chloride anion (Cl^-) is significant physiologically because it is essential for the maintenance of fluid and electrolyte balance, and it is needed for the formation of hydrochloric acid in the gastric juices.[2] The absorption of chloride ions occurs predominantly in the gastrointestinal tract in association with sodium uptake.[13] Once absorbed, the chloride is distributed primarily to extracellular fluids (e.g., plasma, interstitial fluid, and secretions) and comprises 0.15% of body weight.[14] The quantity of chloride ions excreted is directly coupled to sodium elimination; however, sodium excretion is under hormonal control, and chloride ions passively follow sodium movement.[15] Normally, excretion of chloride parallels consumption and homeostasis is achieved.[13-15]

DIETARY REQUIREMENT

Although the chloride anion is an essential dietary requirement,[2] the minimum adult requirement to sustain human life remains undetermined. In comparison, the estimated safe and adequate daily dietary intake of chloride ranges between 1.7 and 5.1 g. These values are supported by limited information and do not represent actual recommended dietary allowances (RDA) such as those set for other recognized nutrients.[16] However, the normal human diet represents a rich source of chloride (as NaCl), and therefore it is probably ingested in amounts that far exceed the minimum adult requirement.[2] For example, daily consumption of chloride-ions by adults is normally between 5 and 10 g; over this range the quantity of chloride eliminated each day will vary precisely with the amount ingested.[14] Nevertheless, a low concentration of chloride in drinking water will probably not be responsible for adverse health effects if adequate rations are supplied.

HEALTH EFFECTS

Two different types of performance-degrading health effects are possible consequences of an elevated concentration of chloride in drinking-water supplies. A direct effect of the consumption of water containing a large amount of chloride is

laxation. At high concentrations, chloride also affects the taste of water. If the water has an objectionable taste, some water consumers might reduce water intake, which in some circumstances (e.g., desert conditions where large amounts of water are needed to replace sweat losses) could lead to dehydration.

For completeness we note that a recent study by Kurtz and Morris[17] suggests that hypertension in humans may be related to the dietary intake of chloride in association with sodium (i.e., NaCl). Military populations, however, would have to consume high levels of NaCl in field-water supplies for periods longer than one year and have minimal sweat loss during the exposure period to experience any performance-degrading symptoms related to hypertension. Consequently, we do not consider hypertension to be a relevant performance-degrading health effect upon which to base our recommendations for military field-water standards for chloride. The military may want to consider hypertension as a health-effect end point upon which to base future recommendations for standards for fixed installations.

LAXATIVE EFFECTS

Laxative effects that result from the consumption of water containing an elevated concentration of chloride appear to be associated with the process of osmoregulation of fluids in the intestinal tract. For example, the presence of a high concentration of chloride in the intestinal tract probably causes extracellular fluids to flow into the intestinal tract osmotically. This osmotic effect increases both the fluid volume in the large intestine and the motility of the smooth muscle lining the large intestine. Both factors help to flush the large intestine and thereby cause diarrhea.[15] Such laxative effects may be eliminated in some cases if a period of physiological adjustment to high-chloride water is permitted, or if water that contains a low concentration of TDS is ingested soon after consumption of the high-chloride water.

The laxative properties of elevated concentrations of chloride in drinking-water supplies and the osmotic mechanism that appears to be responsible for these effects seem to be confirmed by the following observations. First, Cass[9] reported that a single oral dose of 0.5 L of water containing 7.4 g/L of NaCl (4.5 g/L of Cl^-) can induce a laxative effect in humans. Second, Murray et al.[18] showed that the tendency for human subjects to develop diarrhea after being administered a total of 46 g/d of NaCl (28 g/d of Cl^-) in their diet could be eliminated by their ingestion of a large amount of distilled water. Evidence also indicates that laxative effects can be circumvented by physiological adjustment to high-chloride water. According to Cass[8] and Cass et al.,[6] no serious physiological effects were ever reported to public health authorities in Hawaii and Arizona, even though some

residents used drinking water containing chloride concentrations as high as 1100 mg/L and 1500 mg/L, respectively. Nevertheless, Cass[8] states that individuals normally unaccustomed to such elevated levels of chloride in drinking water may require an acclimation period of a few days to a week to adapt physiologically and to overcome the laxative effects that may occur initially.

TASTE EFFECTS

Bruvold[19] conducted a study in which panelists indicated their behavioral response to the taste of two solutions of NaCl: 1000 mg/L (600 mg/L of Cl^-) and 2000 mg/L (1200 mg/L of Cl^-). The mean behavioral response of the panelists to the taste of 1000 mg/L of NaCl in water was that they might be able to accept the water as an everyday drinking water. However, at 2000 mg/L of NaCl in water, the mean behavioral response rating of the panelists indicated that they might not be able to accept the water as their everyday supply. Zoeteman et al.[20] have shown that water with a bad taste will be consumed in smaller quantities than water with a good taste. This suggests that concentrations of chloride greater than 1200 mg/L in water may make the taste of water so objectionable that people may not want to drink it. Such individuals could become susceptible to dehydration, especially in desert environments, where large quantities of water must be consumed to replace sweat losses. Furthermore, dehydration can lead to discomfort, weariness, muscle weakness, apathy, impaired coordination, delirium, and heat stroke.[21]

DEVELOPMENT OF RECOMMENDATIONS FOR STANDARDS

Unfortunately, the previous data are insufficient to derive quantitatively no-effects threshold levels and comprehensive dose-response relationships for the quantity of chloride that would induce laxative effects. Furthermore, the available data do not adequately address the amounts of other ions that are always present along with chloride in natural waters, and these other constituents may confound any effects attributed to the presence of chloride alone. However, the evidence does suggest that military personnel will probably find the taste of water objectionable when chloride is present in concentrations substantially less than those reported to induce laxative effects. Therefore, military personnel unaccustomed to the taste are likely to refuse to drink water containing an elevated chloride concentration. Consequently, dehydration is considered to be the most likely health effect that may occur when military personnel are exposed to high-chloride water and alternate supplies are not available.

Chloride ions constitute only a portion of the TDS content of water; therefore, elevated chloride concentrations in water reflect the presence of even greater TDS concentrations, and the relationship between the TDS concentration in water and the objectionable taste of water has been quantified by Bruvold and Ongerth.[22] In the absence of comprehensive dose-response data concerning the laxative effect of high chloride concentrations in drinking water, we recommend computing chloride standards for military field-water supplies by equating the chloride concentration to a corresponding TDS concentration. This computation is made by applying the quantitative method developed by Bruvold and Ongerth[22] to determine the portion of the population that could refuse to drink the water because of an objectionable taste produced by its TDS content. The TDS concentration corresponding to the amount of chloride present in a field-water supply is estimated by assuming that the TDS concentration is composed entirely of NaCl. The basis for this assumption is the fact that Na and Cl ions are the predominant constituents of the TDS content of field water, particularly seawater, that has been processed through a ROWPU to achieve potability.[23] This means that for this calculation, the chloride content of military field-water supplies represents approximately 60% of the TDS concentration. This also means that the lower limit of the TDS-to-chloride ratios generally encountered in natural waters equate to the minimal TDS level to be expected for a given chloride level.

METHODOLOGY

The Bruvold and Ongerth[22] approach was based on the use of taste panels to assess the general taste quality of natural waters by methods of psychometric scaling. Two psychometric rating scales, a quality (Q) scale and an action-tendency (AT) scale, were an integral part of this approach. An explanation of the derivation and application of these scales follows.

Derivation of Q and AT Psychometric Rating Scales

The Q and AT rating scales and scale values used by Bruvold and Ongerth[22] were developed by Bruvold[19] in an earlier study. Bruvold constructed them according to the method of equal-appearing intervals described by Edwards.[24] Accordingly, 53 adult subjects were instructed to place each of 34 Q and then 18 AT statements into one of 11 numerically identified categories. The 34 Q statements described the taste of water (e.g., "This water has an excellent taste") and the 18 AT statements referred to the behavioral response of the individual concerning actual consumption of the water (e.g., "I could never

drink this water"). The 11 categories into which these statements were to be placed represented an 11-interval psychological continuum describing degrees of unfavorableness or favorableness for each subject. The subjects were told that degrees of unfavorableness decrease from the 1st to the 5th category, the 6th category is considered neutral, and the degrees of favorableness increase from the 7th to the 11th category. The judgments of three subjects were rejected because these subjects did not divide the statements into the 11 categories in the prescribed manner.[19]

Once all of the subjects separated the 34 Q statements and then the 18 AT statements into the 11 categories, and the judgments of the three previously mentioned subjects were discarded, scale values were derived for each of the statements. The median of the distribution of the 50 judgments obtained for each statement on the 11-interval psychological continuum was used as the scale value for that statement. The median or scale value for each statement was determined from a mathematical equation or directly from a graph of the relationship between the cumulative proportions of judgments and the 11-interval psychological continuum into which the statement was distributed by each of the 50 subjects.[24]

To construct Q and AT rating scales with equal-appearing intervals between scale values, and thereby to reduce the number of statements, the interquartile range was determined first for each statement. This value represents the spread or variation of the middle 50% of the judgments (i.e., the number of intervals between the 25th and 75th percentiles) for a particular statement on the 11-interval continuum. A large interquartile range measurement meant a statement was ambiguous and should be removed from the scale. Additionally, the interquartile range value was used for choosing between two or more statements with equal scale values but unequal interquartile ranges. The interquartile range value for each statement was determined mathematically or graphically in ways similar to those used for determining scale values.[24] In summary, Bruvold[19] used both scale and interquartile range values as the criteria for constructing the Q and AT psychometric rating scales from the original 34 Q and 18 AT statements. The resulting scales were thereby reduced to nine statements with nearly equal distances between scale values and a relatively small interquartile range associated with each statement.[19]

Application of Q and AT Psychometric Rating Scales

The Q and AT psychometric rating scales, which were constructed by Bruvold,[19] were applied by Bruvold and Ongerth[22] using the following procedure. A taste panel of 20 adults (13 male and 7 female) was asked to use the two psychometric rating scales to

evaluate the taste of 29 different natural waters from California. These natural waters contained TDS concentrations ranging from about 50 to 2200 mg/L, levels that represent a typical range for TDS concentration in natural waters. Water samples were presented at room temperature to the taste panelists. According to results from earlier research, sample temperatures between 40°F and 72°F had minimal systematic effect on ratings. The Q scale consisted of the nine Q statements shown in Table 2, which describe the taste of water in qualitative terms. The AT scale contained the nine AT statements shown in Table 3, which refer to the behavioral response of the individual concerning the actual consumption of the water. The 20 taste-panel members were instructed to score natural water samples on both Q and AT rating scales using the scale values associated with each statement that best described their judgment. The mean Q and AT scores were then calculated for each natural water sample from the 20 scores that were recorded.

To evaluate the relationship between the mean Q and AT scores and the TDS concentration corresponding to these mean scores, Bruvold and Ongerth[22] plotted the data and employed linear regression analysis to calculate the lines of best fit through each set of data points. This analysis revealed that an inverse linear relationship exists between taste-quality scores and TDS concentration and between behavioral intention scores and

Table 2. Quality (Q) scale for describing the taste of water.[22]

Statement	Median scale value
This water has an excellent taste.	10.67
This water has a very good taste.	9.79
This water has a good taste.	8.45
This water has a slightly good taste.	7.16
This water has a neutral taste.	6.00
This water has a slightly bad taste.	4.61
Boundary scale value for military unacceptability	3.78[a]
This water has a bad taste.	2.95
This water has a very bad taste	2.05
This water has a horrible taste.	1.16

[a] Scale value representing point where it is assumed that military personnel would refuse to drink the water.

Table 3. Action-tendency (AT) scale for describing a behavioral response to the taste of water.[22]

Statement	Scale value
I would be very happy to accept this water as my everyday drinking water	9.96
I would be happy to accept this water as my everyday drinking water	9.20
I am sure that I could accept this water as my everyday drinking water	8.07
I could accept this water as my everyday drinking water.	7.35
Maybe I could accept this water as my everyday drinking water.	5.64
I don't think I could accept this water as my everyday drinking water.	4.21
Boundary scale value for military unacceptability	3.43[a]
I could not accept this water as my everyday drinking water.	2.65
I could never drink this water.	1.27
I can't stand this water in my mouth and I could never drink it.	1.05

[a] Scale value representing point where it is assumed that military personnel would refuse to drink the water.

TDS concentration. By assuming a normal distribution around each line of best fit and a constant standard error of estimation for each scale, Bruvold and Ongerth[22] showed that the regression equations and the corresponding standard errors of estimation, in combination with z-score equations, could be used to estimate the proportion of people rating water at or below a certain value on the Q or AT rating scale. Thus, this procedure could be used to estimate the percentage of a population that would rate a water unacceptable on the basis of taste and, consequently, TDS content estimated from the chloride ion concentration. Therefore, the chloride standards recommended for military field-water supplies could be expressed quantitatively in terms of the acceptable proportion of troops rating the water at a specific level of unacceptability on the Q or AT rating scale.

ACCEPTABILITY OF MILITARY FIELD-WATER SUPPLIES BASED ON TDS CONCENTRATION

Actual calculation of the TDS standards for military field-water supplies, using the Bruvold and Ongerth[22] procedure, requires the following assumptions. First, the TDS content of the 29 different natural waters used in the taste survey is assumed to represent

the range of TDS concentrations found in the natural or purified waters that are encountered typically by military populations. Second, the taste panel of 20 adults is assumed to have the same taste as military personnel. Third, ratings of the general taste quality of water at or below 3.78 on the Q scale (the boundary scale value for delineating the statement that "This water has a bad taste") and at or below 3.43 on the AT scale (the boundary scale value for delineating the statement that "I could not accept this water as my everyday drinking water")* are assumed to be the critical scale values. These values indicate the point where military personnel will be so dissatisfied with the water supply that they would refuse to drink it or would substantially reduce their water consumption, thereby becoming susceptible to dehydration (see Tables 2 and 3). Finally, a normal distribution is assumed to exist around the lines best fitting the relationship between TDS concentrations and Q and AT values derived by Bruvold and Ongerth,[22] and a constant standard error of estimation is assumed for each scale.

The relationship between TDS concentration computed from the chloride content and the percentage of the population rating water at or below a particular Q or AT scale rating can now be expressed mathematically using the regression equations and standard errors of estimation (derived by Bruvold and Ongerth)[22] in combination with z-score equations. For example, the mean Q or AT rating can be estimated for any water supply by measuring the chloride concentration, computing the TDS content according to the assumptions previously discussed (i.e., chloride represents 60% of the TDS concentration), and then inserting that value into the applicable regression equation:

$$\mu_Q = 7.60 - 0.00213\ [TDS], \tag{1}$$

$$\mu_{AT} = 8.03 - 0.00163\ [TDS], \tag{2}$$

where

μ_Q = mean Q-scale rating;
[TDS] = concentration of total dissolved solids in the water supply; and
μ_{AT} = mean AT-scale rating.

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* Boundary scale values are used because the Q and AT scales are presumed to be continuous. Therefore, the separation between adjacent statement categories is assumed to be at the arithmetic mean scale value between the two statements and not at the median scale value for either statement.

The standard error of estimation for the mean Q-scale rating (σ_Q) is 1.47; the standard error of estimation for the mean AT-scale rating (σ_{AT}) is 1.46. According to these equations, the mean Q- and AT-scale ratings for a water supply containing a TDSconcentration of 500 mg/L (300 mg/L of Cl^-) would be 6.54 and 7.22, respectively. The mean Q-scale rating (μ_Q) of 6.54 indicates that 50% of the population would indicate that the "Water has a neutral taste" or worse, and 50% would indicate that the "Water has a slightly good taste" or better (see Table 2). The mean AT-scale rating (μ_{AT}) of 7.22 indicates that 50% of the population would rate the water acceptable for everyday consumption or better, and 50% would rate the water as "Maybe" they could accept it for everyday consumption or worse (see Table 3). The mean Q-scale rating value and the mean AT-scale rating value indicate the median response for a population because the regression equations describe the lines of best fit for the data from the taste-panel study; as stated previously, a normal distribution is assumed to exist around the lines of best fit.

The mean Q or AT value (μ) can then be incorporated into a z-score equation, along with the respective standard error of estimation (σ) for the Q or AT scale, and the respective scale value that represents the point on either scale at or below which it is assumed that military personnel could refuse to drink the water (i.e., Q = 3.78 and AT = 3.43). Thus, the solution to the *z*-score equation is a standard normal deviate that corresponds to the proportion of the population on each scale that would refuse to drink the water based on its taste.

For example, the z-score equation is expressed as

$$z_{\%} = \frac{x - \mu}{\sigma}, \qquad (3)$$

where

$z_{\%}$ = standard normal deviate corresponding to a percentage of the population;
x = Q or AT rating corresponding to the scale value at or below which military personnel will score the water supply after tasting it, (i.e., $x_Q = 3.78$ and $x_{AT} = 3.43$ for the case where military personnel will refuse to drink the water);
μ = mean Q- or AT-scale rating calculated from Eqs. 1 or 2, respectively; and
σ = standard error of estimation for Q- or AT-rating scale (i.e., $\sigma_Q = 1.47$ and $\sigma_{AT} = 1.46$).

For a water supply containing a TDS concentration of 500 mg/L (300 mg/L of Cl^-), the standard normal deviates are -1.88 and -2.60 for the Q and AT scales, respectively. The percentage of the population corresponding to each standard normal deviate

is determined from a table of values for the standard normal distribution.[25] Based on the standard normal deviate calculated from the mean Q value corresponding to a TDS concentration of 500 mg/L, the percentage of the population that will complain about the bad taste of the water and refuse to drink it ($x_Q = 3.78$) is estimated to be about 3%. Based on the standard normal deviate calculated from the mean AT value corresponding to a TDS concentration of 500 mg/L, the percentage of the population that could not accept the water because of its poor taste ($x_{AT} = 3.43$) is estimated to be approximately 0.5%.

The z-score equation can also be used to estimate the Q or AT value at or below which a certain proportion of the population will rate the water. According to this application of the z-score equation, when the water supply contains 500 mg/L of TDS and the rating score for 10% of the population is of interest, then $z_{\%} = -1.28$ and x equals 4.66 for the Q value and x equals 5.35 for the AT value (see Tables 2 and 3 for closest corresponding statements).

Calculations similar to those described previously were used to construct the graphs in Figs. 1 and 2. Figures 1 and 2 show the relationship between TDS concentration and the percentage of the military population rating water unacceptable on the Q (≤ 3.78) and AT (≤ 3.43) scales, respectively, and therefore at risk of refusing to drink the water because of an objectionable taste produced by the TDS concentration in the water. Both Figs. 1 and 2 could be used to calculate TDS standards, or in this case chloride standards, once a percentage of military personnel at risk of dehydration has been defined. However, the fact that the slopes of the AT lines in Fig. 2 are not as steep as the slopes of the Q lines in Fig. 1 suggests that people may actually accept water that has a poor taste quality, as Bruvold and Ongerth[22] indicated in their paper. This means that the AT scale is the most appropriate one to use for determining chloride standards based on TDS concentrations, although military personnel may still complain about the taste of water even if they do drink it. Thus, the AT lines in Fig. 2 are best suited for estimating the proportion of the military population that would refuse to drink the water and thereby become susceptible to dehydration.

RECOMMENDATIONS FOR STANDARDS

Table 4 shows a comparison between three chloride concentrations, the estimated TDS concentration computed for each, and the corresponding percentages of military personnel who would refuse to drink the water ($AT \leq 3.43$) or would complain about bad taste ($Q \leq 3.78$). These three chloride concentrations represent possible standards for chloride concentrations in military field-water supplies. Currently, the U.S. Army

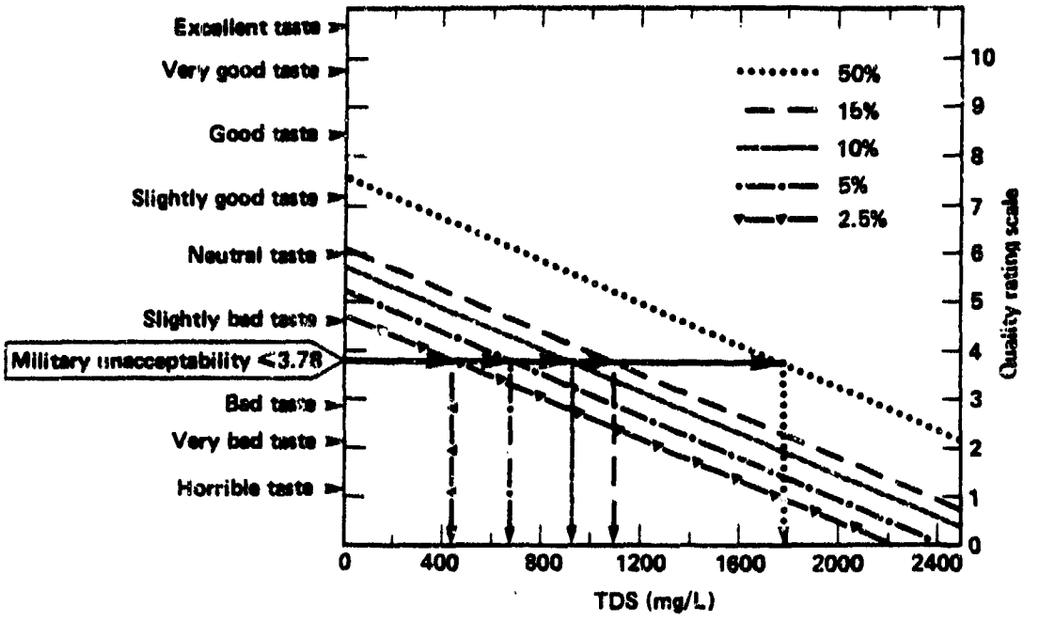

Figure 1. Relationship between TDS concentration and percentage of military population rating water unacceptable on the quality (Q) rating scale (i.e., ≤ 3.78, the boundary scale value defining military unacceptability). Extrapolated from analyses by Bruvold and Ongerth[22] of the taste-panel responses to California water supplies.

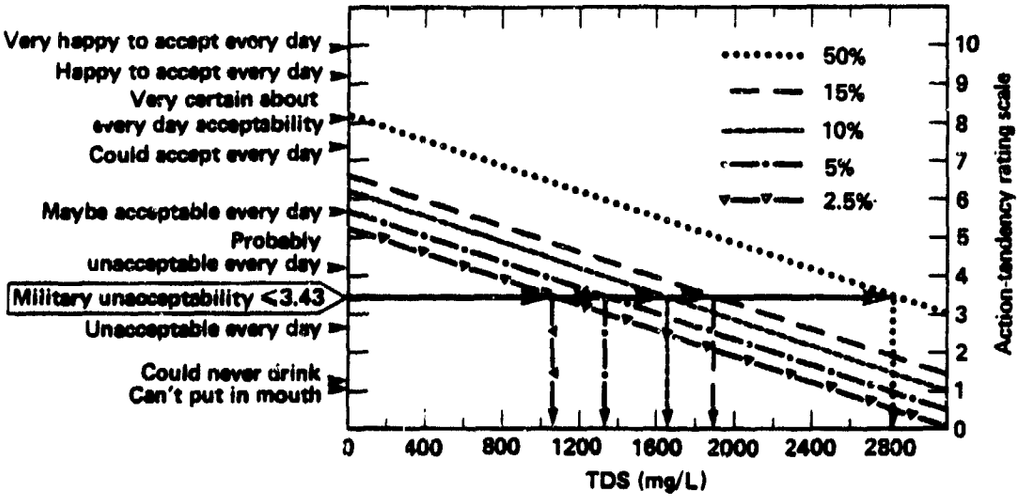

Figure 2. Relationship between TDS concentration and percentage of military population rating water unacceptable on the action-tendency (AT) rating scale (i.e., ≤ 3.43, the boundary scale value defining military unacceptability). Extrapolated from analyses by Bruvold and Ongerth[22] of taste-panel responses to California water supplies.

field-water standard for chloride is 600 mg/L,[26] and the TDS concentration associated with this amount of chloride is estimated to be 1000 mg/L. Thecorresponding percentage of the military population that would consider this water unacceptable for consumption would be about 2%, whereas approximately 12% of the military population would complain that this water has a bad taste. Increasing the chloride standard to 900 mg/L means that the TDS content is estimated to be about 1500 mg/L. At this chloride concentration and estimated TDS level, the proportion of the military population that would refuse to drink the water would increase to nearly 7%, and approximately 34% of the military population would complain about the bad taste of the water. Finally, a chloride standard of 1000 mg/L would correspond to an estimated 1700 mg/L of TDS. At this concentration of TDS, approximately 11% of the military population would refuse to drink the water, and the military population complaining about bad taste could be as high as 44%. Of course, achieving chloride concentrations less than 600 mg/L (i.e., TDS less than 1000 mg/L) would facilitate consumption of adequate amounts of water by military personnel, particularly when military operations are conducted in arid regions.

The data presented in Table 4 indicate that the current chloride standard for military field-water supplies, 600 mg/L for both short-term (7-d) and long-term (1-y)

Table 4. Comparison between chloride and corresponding TDS concentrations, considered as possible standards for military field-water supplies, and estimated proportions of military population refusing to drink the water or complaining that it has a bad taste.

Possible chloride standard in field water (mg/L)	Estimated TDS concentration (mg/L)[a]	Proportion of military population (%)	
		Refusing to drink water	Complaining about taste of water
600[b]	1000	2.1	12
900	1500[c]	6.9	34
1000[d]	1700	11	44

[a] Calculated by assuming that sodium and chloride are the only two constituents of TDS, which is based on the fact that dissolved solids in ROWPU product water are composed almost entirely of Na and Cl ions.[23]

[b] Current chloride field-water quality standard used by the military.[26]

[c] Current TDS field-water quality standard used by the military.[26]

[d] Chloride concentration consumed by populations in Hawaii and Arizona without public health authorities reporting health-effec consequences.[6,8]

exposure periods, should be retained; at this concentration, only a small percentage of troops are predicted to refuse to drink the water (approximately 2%), and the proportionof troops complaining about the taste of water is limited to about 12%. The higher chloride concentrations presented in Table 4 could also be considered as standards if the U. S. Army is willing to accept a greater proportion of troops at risk of refusing to consume the water and therefore becoming susceptible to dehydration. Furthermore, a high percentage of troops (>44%) would be complaining about the bad taste of the water at chloride concentrations exceeding 1000 mg/L, and this may represent a serious morale problem.

We obtained results similar to those presented in Table 4 when we used multiple-regression equations, in combination with z-score equations, to estimate the proportion of the military population refusing to drink water and complaining about the taste of water containing TDS composed entirely of sodium and chloride. In our calculations we estimated mean Q and AT values based on the contribution of the individual ionic constituents of TDS specifically. Bruvold[27] derived these multiple-regression equations from the unpublished results of a taste-panel study he conducted on February 7, 1968. We simplified his multiple-regression equations into the following expressions:

$$\mu_Q = 7.96 - 0.0851[\text{mg/L Na}] + 0.0520[\text{mg/L Cl}] , \quad (4)$$

and

$$\mu_{AT} = 8.47 - 0.0608[\text{mg/L Na}] + 0.0357[\text{mg/L Cl}] . \quad (5)$$

The standard error of estimation for the mean Q-scale rating (σ_Q) in Eq. 4 is 1.44; the standard error of estimation for the mean AT-scale rating (σ_{AT}) in Eq. 5 is 1.43.

Equations 4 and 5 were simplified because we assume that the TDS concentration is composed entirely of sodium and chloride ions. For purposes of these calculations, sodium comprises 39.4% of the TDS, and chloride comprises 60.6%. Thus, a TDS concentration of 1000 mg/L contains 394 mg/L of sodium and 606 mg/L of chloride; a TDS concentration of 1500 mg/L contains 591 mg/L of sodium and 909 mg/L of chloride; and a TDS concentration of 1700 mg/L contains 670 mg/L of sodium and 1030 mg/L of chloride. The corresponding proportions of military personnel that might refuse to drink such waters are 2.1, 12, and 21%, respectively; the corresponding proportions of military personnel that might complain about the taste of such waters are 6.7, 21, and 31%, respectively. The similarity between those results using the multiple-regression equations for specific ions

and those results obtained using the linear regression equations for TDS (see Table 4) suggests that it is reasonable to use TDS to approximate the response of military personnel to chloride concentrations in drinking water.

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CHAPTER 5. MAGNESIUM

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ABSTRACT

The objective of this chapter is to develop and recommend a drinking-water standard for the magnesium ion (Mg^{+2}). High levels of magnesium in water are of concern because they can produce diarrhea and thereby disrupt the normal water balance of military personnel, particularly in hot climates. We determined a no-effects concentration by estimating a single no-effect dose and calculating the concentration that would result if the dose were diluted into the volume of water suggested. Thus, the recommended standard for Mg^{+2} is 30 mg/L for a water consumption rate of 15 L/d, and 100 mg/L for a water consumption rate of 5 L/d.

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INTRODUCTION

The purpose of this research was to develop a recommendation for the maximum allowable concentration of magnesium in drinking water, for water consumption rates of 5 and 15 L/d. The assumption that a soldier will drink 15 L of water in a day is based on water-consumption studies on men performing physical labor in hot climates and on the basis of U.S. Army field experience in desert situations. The 5-L/d consumption rate is considered reasonable for less severe situations. A standard is needed because high levels of magnesium in drinking water can cause diarrhea. Military experience shows that diarrhea can be incapacitating and can contribute to the dehydration problems that frequently occur in arid environments.

First, we discuss some of the chemical properties, likely sources, and methods for measuring magnesium concentrations. This information should be of value to personnel responsible for locating raw-water sources and operating and monitoring the water-treatment equipment. Second, we describe the pharmacokinetic considerations pertinent to setting a standard for magnesium and understanding its effects. Third, we identify and describe the health effects associated with magnesium. This background information that is necessary for developing a standard could be of value to personnel who are responsible for evaluating the hazards of specific field situations.

In developing the standard, it was necessary to make some assumptions. In addition, some uncertainties are apparent in the data on which the recommended standard is based. Every attempt has been made to identify the uncertainties and make the assumptions explicit.

GENERAL PROPERTIES

Magnesium (Mg) comprises about 2.1% of the earth's crust, making it the eighth most abundant element.[1] It is also widely distributed among the minerals and soils of the crust, commonly existing in combination with carbonate, silicate, sulfate, and chloride.[2] Like the other alkaline-earth elements, Mg is not found in nature in its metallic form because it is an active reductant that will react with a variety of nonmetals.[3]

Magnesium generally loses both of its outermost valence electrons and becomes a bivalent cation (Mg^{+2}).[4] The magnesium cation is important when considering water quality because it is one of the principal cations causing hardness.[5] Most salts of magnesium are water-soluble; an exception is magnesium hydroxide, $Mg(OH)_2$, which is only soluble to the extent of 19 mg/L at 18°C.[2,4] Table 1 shows levels of magnesium

Table 1. Magnesium levels found in natural waters.

Mg concentration (mg/L)	Description of water	Reference
~4 (avg.)	Natural fresh water	1
	Mineralized ground water in	
1.5 to 157	South Dakota; TDS > 2,000 mg/L	6
242	Hot spring; TDS = 1,580 mg/L	7
1350	Seawater; TDS ~ 35,000 mg/L	1
	Brine ground water, Eddy County,	
2490	New Mexico; TDS = 329,000 mg/L	7

found in several different types of natural waters. In two surveys of the mineral content of natural water in the United States, magnesium levels exceeded 100 mg/L infrequently; and neither survey reported levels exceeding 200 mg/L, even in fresh waters high in total dissolved solids (TDS >2000 mg/L).[6,8] In a survey of the drinking-water supplies of 70 Canadian municipalities, the magnesium concentration in raw water never exceeded 82 mg/L.[9] Assuming that brine will not be used as a water source, seawater probably poses the greatest challenge to treatment equipment for magnesium-ion removal.[1]

METHODS FOR DETECTING MAGNESIUM

Magnesium levels can be measured in water using atomic absorption spectroscopy, gravimetric methods, or colorimetric tests.[10,11] Because the colorimetric tests are the fastest and do not require large pieces of equipment, they are easily used in the field. The magnesium concentration can be calculated once the magnesium hardness is known. Magnesium hardness is calculated by measuring total hardness and subtracting the results of the test for calcium hardness.[5,11] The U.S. Army has colorimetric test kits for measuring both total hardness and calcium hardness.[11]

PHARMACOKINETICS

Pharmacokinetic considerations are important to the establishment of a drinking-water standard for magnesium because they show that any systemic effects caused by a magnesium imbalance result from causes other than the ingestion of too much magnesium.

ABSORPTION

Most absorption of ingested magnesium occurs in the small intestine and a small amount also occurs in the colon.[12] Absorption takes place almost entirely by a saturable mechanism, such as facilitated diffusion or active transport.[13] Thus, only a limited number of carrier proteins are available for transporting magnesium ions from the intestinal lumen, through the mucosal lining of the intestine, and into the blood serum. However, a small fraction of ingested magnesium may be absorbed by passive diffusion through the cell membranes of the intestinal mucosa. This small fraction (~10%) of the absorbed dose would have linear absorption kinetics,[13] but the dominance of magnesium absorption by a saturable process is consistent with findings that the fraction of ingested magnesium that is absorbed decreases at high-dose levels. For example, one study reported absorption percentages of 75.8, 44.3, and 23.7 for orally administered magnesium doses of 23, 240, and 564 mg/d, respectively.[14] At the normal magnesium-ingestion rates of adults in the U.S. (240 to 480 mg/d), the absorbed fraction is about one-third to one-half of the total amount ingested.[12,15]

Antagonistic interactions that involve magnesium and another substance can affect the absorption of either magnesium or the other substance. For example, calcium and magnesium are believed to be competitive with respect to their absorptive sites. Thus, high calcium levels in the intestinal tract can reduce magnesium absorption.[16] Alternatively, magnesium, administered as $MgCl_2$, reduces fluoride absorption, according to experiments with rats.[17]

ELIMINATION

Ordinarily, most ingested magnesium is not absorbed from the lumen of the intestines and thus is eliminated in the feces.[18] For absorbed magnesium, the kidney is the major route of excretion, accounting for the elimination of nearly all serum magnesium.[18,19] Smaller amounts are normally eliminated via sweat, milk, and secretions into the intestinal tract.[16] However, the normal amounts of magnesium eliminated

through each route can change. For example, one study involving humans found that under desert conditions, sweat accounted for about 12% of the total-magnesium excretion during the day; if nighttime sweat losses were considered, sweat accounted for 25% of the total.[20]

Normally, magnesium in the serum is filtered into the glomerulus and then reabsorbed from the tubules of the kidney to the extent that only 3 to 5% of the filtered magnesium is expected in the urine.[21] When magnesium levels are elevated, clearance increases linearly with the serum level.[19] Magnesium elimination by the kidneys and the maintenance of a constant magnesium level in the serum appears to be controlled by both hormonal and nonhormonal factors.[21]

DISTRIBUTION

The body of an average 70-kg person contains approximately 24 g of magnesium: 50% in bone, 45% as intracellular cation, and 5% in the extracellular fluid.[12] Intracellular and extracellular magnesium concentrations can vary independently; and even though 30% of the magnesium in the skeleton is an exchangeable pool, mobilization from this pool is a slow process in adults.[12] The normal range of magnesium blood levels deviates from the mean by less than 15%, indicating that a sensitive control mechanism is operating.[22] About one-fourth of blood magnesium is bound to protein and is nondiffusible. The remaining three-quarters is diffusible and appears in the glomerular filtrate.[21]

ESSENTIALITY

Magnesium is an essential human nutrient required as a co-factor for many enzymes and is contained in many metalloenzymes. It also plays an important role in neurochemical transmission and muscular excitability.[12,16,23] The National Academy of Sciences' recommended dietary allowance for magnesium is 350 mg/d for adult males and 300 mg/d for adult females.[23]

HEALTH EFFECTS

The ability of magnesium to cause laxative effects is well established: it is widely prescribed as a laxative and cathartic. Therefore, it is reasonable to expect that consumption of high levels of magnesium in drinking water would cause laxative effects. In addition, magnesium is associated with other health effects--hypermagnesemia and magnesium deficiency--and it has adverse effects on the palatability of water.

LAXATIVE EFFECTS

Magnesium salts are used commonly as laxatives and cathartics; in clinical medicine, 40 meq (480 mg) is the recommended dose when a laxative effect is desired.[24] However, as with other saline laxatives, it appears that humans can develop a tolerance to magnesium's laxative effects.[1]

The World Health Organization (WHO) states that one possible undesirable effect of water with high magnesium content is gastrointestinal irritation, especially in the presence of sulfate.[25] Drinking-water supplies high in magnesium have been associated with elevated levels of laxative problems in the community consuming the water.[6,26] Laxative problems can be dangerous to the soldier because, if severe enough, they can be incapacitating. However, they can also be dangerous before that point by disrupting the normal water balance and accelerating dehydration. It is this degree of laxative effect that should be protected against to ensure no performance degradation on the part of a soldier.

Saline cathartics, such as magnesium salts, cause the retention of excess fluid in the intestinal lumen and increased motor activity in the intestinal tract (hyperperistalsis). Traditionally, this has been explained as poorly absorbed, but soluble, ions exerting an osmotic pressure that causes the retention of fluid in the intestinal lumen. This increase in bulk indirectly stimulates intestinal transit.[24] More recent studies report that the cause of the laxative effects of various saline solutions can be much more complicated. For example, in addition to osmotic effects, saline cathartics may increase the fluid volume of the intestinal tract by reducing water absorption in the small intestine and by stimulating substantial increases in the secretion of pancreatic, gastric, and intestinal fluids. It is not clear to what extent these effects are caused directly by the various ions of the saline cathartics or to what extent they are mediated by the cathartic-stimulated release of hormones, particularly cholecystokinin.[27-29] The same uncertainty exists in understanding how hyperperistalsis is induced.[27,29] Consequently, it appears that at least some of the saline cathartics have a fairly complex mode of action and can cause laxative effects by several different mechanisms.

HYPERMAGNESEMIA

No evidence was found to indicate that large oral intakes of magnesium are harmful to people with normal renal function.[1] Thus, toxic effects following oral administration of magnesium are rare, attributable primarily to the body's ability to sustain remarkably constant serum-magnesium levels.[16] The National Research Council Safe Drinking Water

Committee[1] reports that hypermagnesemia occurs in humans only as a result of kidney malfunction. For example, if the glomerular-filtration rate falls below 30 mL/min, magnesium excretion will be impaired and serum levels may rise to undesirably high levels.[30] One of the possible causes of a sudden drop in the glomerular-filtration rate and the appearance of hypermagnesemia is dehydration.[12]

The symptoms associated with elevated plasma levels of magnesium include muscle weakness, hypotension, sedation, confusion, and respiratory paralysis; electrocardiogram changes have also been reported.[12,16] The normal plasma concentration of magnesium is 1.5 to 2.2 meq/L.[12] As plasma levels begin to exceed 4 meq/L, the deep-tendon reflexes are diminished; they may disappear at levels of about 10 meq/L. At 12 to 15 meq/L, respiratory paralysis becomes a potential hazard. The plasma concentration of magnesium that causes complete heart block may be variable.[12]

MAGNESIUM DEFICIENCY

The effects of magnesium deficiency include neuromuscular irritability, calcification, and cardiac and renal damage.[16] However, substantial quantities of magnesium are present in a variety of foods; consequently, magnesium deficiencies attributable to inadequate amounts of its ingestion appear to be rare.[23] Deficiencies can be caused by abnormally high elimination rates, and magnesium deficiencies have been reported that result from diarrhea[12] and the performance of hard labor in hot climates (i.e., loss through perspiration).[1]

ADVERSE EFFECTS ON WATER PALATABILITY

Palatability of drinking water is important to military personnel because an objectionable taste could discourage a soldier from drinking as much water as is needed and thus contribute to voluntary dehydration in an arid environment. The taste threshold of a substance in water is often recommended as a standard for substances that can give water a bad taste. However, evidence exists that demineralized water has an unpleasant taste and that the taste threshold for mineral ions is actually at or very near the concentration that people report as having the most pleasant taste.[31] Thus, the concentration at which the taste becomes objectionable appears to be a valid point to recommend as the maximum allowable concentration of a substance in drinking water.

However, the current state of knowledge about the taste qualities of inorganic ions makes it difficult to quantify the contribution that an individual ion, such as magnesium, will make toward degrading the taste of drinking water. Primarily, this difficulty is

presented because ions cannot be tested individually in water and because the nature of the combined effect of several ions on taste is poorly understood. For example, some authors conclude that the taste effects of anions are simply additive to those of cations in taste ratings,[32] but others maintain that anions can mask the taste effects of cations.[33]

In any case, it appears that high levels of magnesium will give a bad taste to water. It also appears that the level of magnesium that people report as having an objectionable taste is affected by the anion with which it is associated.[33-36] In addition to the level and combination of ions, other variables such as psychosocial factors and water temperature can affect the acceptability of a mineralized water.[35,37,38] Also, a wide range of difference exists among individuals (1) in subjective taste intensities reported for a given water,[37,39] and (2) in concentrations that are assessed as acceptable for one's daily drinking water.[40] In the determination of objectionable taste levels another factor is important: people who drink highly mineralized water adapt to the taste of it over time.[41]

Thus, to encourage troops to drink adequate amounts of water, and to prevent voluntary dehydration, the water should not have an objectionable taste. It is generally recognized that at high concentrations, magnesium and other ions will give an unpleasant taste to water. However, the relationship between ion concentrations, drinking water acceptability and the phenomenon of voluntary dehydration is not understood well enough to predict the concentration of any one ion that will begin to exacerbate voluntary dehydration in troops under arid conditions. Some rough guidance can be found in the report that water with a magnesium salt ($MgSO_4$) concentration of 1000 mg/L (magnesium ion concentration would be 200 mg/L) was rated as acceptable by a group tasting the water, even though they also reported that the taste was not good.[34]

DEVELOPMENT OF RECOMMENDATIONS FOR STANDARDS

Major uncertainties are apparent in the method for calculating the recommended standard for magnesium. In addition, assumptions were required to bridge gaps in the current knowledge about the health effects of magnesium.

METHOD AND RATIONALE

Based on the previous discussion of health effects associated with magnesium at the lowest dose, laxative effects are those that lead to performance degradation. In addition, because of the body's ability to maintain a constant magnesium level, and because reports of chronic toxicity are lacking, it is suggested that a long-term (1-y) standard for

magnesium is not necessary and that the recommended standard applies to any exposure period of 1 d or more. The recommended standards in this document are intended to prevent laxative effects from occurring as a result of the consumption of drinking water containing magnesium ions. For a drinking-water consumption rate of 5 L/d, a 100-mg/L standard is recommended; and for a consumption rate of 15 L/d, a 30-mg/L standard is recommended. These are the Mg^{+2} concentrations that result if a laxative dose (480 mg)[24] of magnesium ions is dissolved in the assumed daily water requirement of 5 and 15 L per person, respectively. Another assumption is that magnesium in food will be assimilated or eliminated without causing any laxative effects, and that any laxative effects will be attributable to the additional magnesium ions that are ingested from drinking water.

CALCULATION OF RECOMMENDATIONS FOR STANDARDS

The calculations for the assumed water-consumption rates of 15 L/d and 5 L/d are shown below. The calculation for a 5-L/d water-consumption rate is included because under some non-worst-case conditions, 5 L is a more reasonable amount of water to expect someone to consume in one day. In addition, this allows comparison with other military drinking-water standards, which assume a daily water consumption of 5 L.

$$\frac{480 \text{ mg/d}}{15 \text{ L/d}} = 30 \text{ mg/L} \; ; \text{ and}$$

$$\frac{480 \text{ mg/d}}{5 \text{ L/d}} = 100 \text{ mg/L} \; .$$

MAJOR UNCERTAINTIES AND ASSUMPTIONS

The most important uncertainties in the previous calculation are (1) those associated with the choice of 480 mg as the maximum allowable dose of magnesium that a person can ingest from drinking water each day, (2) those associated with extrapolating from a single dose of 480 mg to multiple doses that total 480 mg, and (3) those associated with the laxative properties of other solutes in the water. Additionally, the recommended standards may be somewhat low, depending on whether or not accumulated individual doses of magnesium totaling a toxic dose would exert the same effect as a single toxic dose. For example, laxatives generally are administered clinically in single doses but a toxic dose of magnesium may only be achieved from drinking water over the course of a day and therefore elimination over time may lead to a different outcome. Consequently,

further research is necessary to resolve the uncertainty associated with whether or not a cumulative toxic dose of magnesium achieved from repetitive drinks would elicit the same laxative response as a single toxic dose. Until such data are available we assume that the effects are similar from the two rates of administration, which leads to conservative recommended standards.

Maximum Allowable Dose

The low doses of the magnesium salts that are prescribed for producing a laxative effect are usually 40 meq (480 mg) of magnesium ions.[24] However, quantitative dose-response data for the laxative effects of magnesium ions are sparse. Consequently, there is some uncertainty about the strength of the laxative response to be expected from a 480-mg dose of magnesium ions. The 40-meq (480-mg) dose is generally prescribed for fasting individuals, a group that is more sensitive to saline laxatives than are nonfasting individuals.[42,43] Even among fasting individuals, there is a wide range in the magnitude of individual responses to a given dose.[44]

Magnesium from Food

According to the National Research Council Safe Drinking Water Committee, the average adult in the U.S. consumes between 240 and 280 mg of magnesium each day, and the average U.S. water supply contains 6.25 mg/L of magnesium.[1] Thus, drinking water typically contributes approximately 3 to 5% of the civilian's magnesium intake, assuming 2 L/d of water consumption. Ingestion of the recommended maximum dose of 480 mg would then increase a typical daily magnesium-ingestion rate by two or three times. The assumption here is that the amount of magnesium in a typical diet normally will not cause a laxative effect, but that a two- to threefold increase caused by ingestion of drinking water high in magnesium will cause such an effect.

Single-Dose to Multiple-Dose Extrapolation

By diluting the one-time 480-mg dose of magnesium ions in the amount of water consumed during one day, the assumption is made that either the ions themselves or an effect produced by the ions will accumulate over a one-day period.

Effects of Other Solutes

The effect of other solutes in the water, in addition to magnesium, is an important uncertainty in predicting the laxative potency of water with a high magnesium concentration. This is because other solutes in the water will also contribute to the osmotic pressure inside the gut and because other ions may induce laxation by physiological mechanisms. Thus, the laxative effects of a high-magnesium water are likely to be supplemented by solutes other than magnesium ions, and they are difficult to predict.

RECOMMENDATIONS FOR STANDARDS

Table 2 is a list of magnesium standards that have been recommended by various groups. Based on our assessment of the available data base, we recommend that the standard for Mg^{+2} in field-water supplies be set at 100 mg/L for a consumption rate of 5 L/d and 30 mg/L for a consumption rate of 15 L/d. Unfortunately, because the standards that have been recommended previous to this study did not include descriptions of how the standards were developed, a comparison of methods is not possible. It should be noted that all of the recommended standards are not based on the same daily rate of water

Table 2. Comparison of recommended drinking-water standards for magnesium ion.

Recommended standard (mg/L)	Assumed water consumption (L/d)	Source
30	15	Maximum concentration recommended by this study
100	5	Maximum concentration recommended by this study
125[a]	2	U.S. Public Health Service (1946)[45]
150[b]	5	QSTAG-245[46]
150	--[c]	TB MED-229[47]
150	2	WHO[25]

[a] The 1962 Public Health Service Standards do not include a Mg^{+2} standard.[41]

[b] Minimum treatment requirement for assuring potability for long-term consumption (>7 d)

[c] Assumed consumption rate for purposes of calculating a recommended standard is not specified.

consumption. The latest edition of the quadripartite military agreement between American, British, Australian, and Canadian forces recommends that if a water-consumption rate larger than 5 L/d is expected, then the recommended concentration for toxic substances in the water should be reduced accordingly.[46] Thus, if the 150-mg/L concentration recommended in the quadripartite agreement is linearly extrapolated from a 5-L/d to a 15-L/d water-consumption rate, the recommended standard would be 50 mg/L. This concentration is more than 50% higher than the level recommended by the method used in this document.

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CHAPTER 6. SULFATE

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ABSTRACT

The purpose of this chapter is to develop and recommend a drinking-water standard for sulfate (SO_4^{-2}) in military field-water supplies. High levels of sulfate are of concern because they can produce diarrhea and thereby disrupt the normal water balance of soldiers, particularly in hot climates. We determined a no-effects concentration by estimating a single no-effect dose and calculating the concentration that would result if the dose were diluted into the volume of water suggested to be consumed daily by military personnel. Thus, the recommended standard for SO_4^{-2} is 100 mg/L for a water-consumption rate of 15 L/d, and 300 mg/L for a water-consumption rate of 5 L/d.

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INTRODUCTION

The purpose of this research was to develop a recommendation for the maximum allowable concentration of sulfate ion in drinking-water, for water-consumption rates of 5 and 15 L/d. The assumption that a soldier will drink 15 L of water in a day is thought to be reasonable on the basis of water-consumption studies of men performing physical labor in hot climates and on the basis of U.S. Army field experience in desert situations. The 5-L/d consumption rate is considered reasonable for less severe situations. A standard is needed because high levels of sulfates in drinking water can cause diarrhea. Military experience shows that diarrhea can be incapacitating and can contribute to the dehydration problems that frequently occur in arid environments.

In this chapter we discuss some of the chemical properties, likely sources, and methods for measuring sulfate concentrations. This information should be of value to the personnel responsible for locating raw-water sources, and operating and monitoring the water-treatment equipment. We also describe the pharmacokinetic considerations that are pertinent to understanding the effects of sulfate. Furthermore, we identify and describe the health effects that have been associated with sulfates. This background information is necessary for developing a standard, and it could be of value to field and preventive medicine personnel responsible for evaluating the health consequences of specific field situations.

In developing the standard we make some assumptions; in addition, there are some uncertainties in the data on which the recommended standard is based. Every attempt has been made to identify the uncertainties and make the assumptions explicit.

GENERAL PROPERTIES

The sulfate ion (SO_4^{-2}) is one of the major anions occurring in virtually all natural waters[1] and may be associated with a variety of different cations. The sulfates of lead and barium are relatively insoluble, but most inorganic sulfates are quite soluble. Sulfate ions can be present in water that has been in natural contact with sulfur-bearing minerals, or they can be present as the result of several different human activities. One of the most common sources is leaching of sulfate salts from evaporite sediments comprised of the sulfates of sodium, magnesium, or calcium.[2,3] Metal sulfides (e.g., iron pyrite), common in igneous or sedimentary rocks, can be oxidized and can also contribute to a water's sulfate load; this is frequently a problem with drainage water from mines.[2] The degradation of natural or anthropogenic organic matter is another source of sulfate in water.[2] For example, the degradation of detergents is known to add substantial quantities

of sulfate to waste waters.[3] Finally, sulfate contamination is known to come from the waste waters of tanneries, sulfate-pulp mills, textile mills, and other industrial processes that use sulfates or sulfuric acid.[2]

In surveys of drinking-water supplies in the U.S., only about 3 to 4% of the supplies tested had sulfate levels in excess of 250 mg/L, the maximum level recommended by the U.S. Public Health Service.[2] The mean sulfate level in the sampled waters was 45 mg/L. Thus, it appears that most people in the U.S. are accustomed to drinking water with fairly low sulfate levels. Table 1 shows the highest sulfate concentrations reported to date for natural waters. In some areas, it may be necessary to use source water with sulfate levels nearly twice that found in seawater.

METHODS FOR DETECTING SULFATE

Sulfates in the concentration range of recommended standards can be detected and measured in water by using the Army's Sulfate Test Kit. With this method, standard solutions are added to the sample, and color changes are observed.[9] Standard Methods for the Analysis of Water and Wastewater[10] describes two gravimetric techniques and a turbidimetric technique, but these require equipment such as ovens and photometers, which may not be readily available during military field operations.

Table 1. Sulfate concentrations reported in natural waters.

Sulfate concentration (mg/L)	Description of water	Reference
46	Mean from survey of U.S. drinking waters (range: 1 to 770)	2
2,712	Seawater	4
4,400	Wellwater, British Somaliland	5
25 to 4,476	Springwater, U.S.S.R.	6
14 to 5,010	Wellwater, North Dakota	7
11,700	Brine, New Mexico	8

PHARMACOKINETICS

The saline purgatives, such as sulfate salts, are poorly absorbed from the digestive tract, although some absorption of component ions does occur.[11] No quantitative description of sulfate-ion absorption was found in the literature; however, sulfates increase the absorption of fluoride from the intestinal tract in rats.[12] Sulfate plays an important role in human metabolism, notably as a moiety that is attached (conjugated) to a variety of natural metabolites or foreign substances, thereby enhancing their water solubility and elimination.[13]

HEALTH EFFECTS

The ability of sulfate salts to cause laxative effects is well established; they are widely prescribed as a laxative and cathartic. The case reports and surveys we describe are limited but do indicate that high levels of sulfate in drinking water will cause laxative effects, especially in people not accustomed to drinking high-sulfate water. The mechanism by which sulfate ions cause laxative effects appears to be fairly complex and is not fully understood. Evidence also suggests that consumption of sulfates in drinking water does not cause any chronic health problems, but high sulfate levels can adversely affect the palatability of water.

LAXATIVE EFFECTS

Sulfate salts induce a laxative effect in individuals ingesting sufficient quantities. A 15-g dose of hydrated magnesium sulfate ($MgSO_4 \cdot 7H_2O$) or its equivalent (e.g., $Na_2SO_4 \cdot 10H_2O$) will produce a cathartic response including a semifluid or watery evacuation in 3 h or less.[11] Doses lower than 15 g produce a laxative effect with a longer latency period. For example, 5 g of hydrated magnesium sulfate administered in dilute solution to a fasting individual is reported to produce "a significant laxative effect."[11] New users of a water supply high in sulfate may report diarrhea and a feeling of heaviness in the stomach.[14,15]

The cation associated with the sulfate appears to have some effect on a sulfate salt's potency as a laxative. For example, calcium sulfate is reported to be much less potent as a laxative than sodium sulfate or magnesium sulfate[16]; and magnesium sulfate is reported to be a better purgative than sodium sulfate.[17] This may result partly from

laxative properties of the cations themselves or from differences in the solubility products of the salts. (See discussion on mechanism of action below.) Other anions, such as phosphate and tartrate, produce weaker laxative effects than sulfate.[18]

Acclimation

People appear to acclimate to the laxative effects of sulfates in a fairly rapid manner[16]; however, it is unknown how rapidly this adaption is acquired or lost. Evidence of acclimation comes mainly from reports that people new to using water supplies high in sulfates are less tolerant to the laxative effects than people who have been using the water supply for protracted periods.[3,14,16,17] Furthermore, there is widespread use of many public water supplies containing high levels of sulfates, and the absence of reported widespread problems also suggests that people can adapt to high sulfate levels.[2,3,6,14-16]

However, even people accustomed to high-sulfate water can apparently suffer a laxative effect if the sulfate concentration suddenly increases. The best documented case of this is in a report from the U.S.S.R. According to this report, the sulfate level in the water supply of a Soviet community suddenly increased from 571 to 1235 mg/L, and 85% of the water's users reported developing diarrhea after drinking the water.[15] (Concomitant increases in solid residues of 1330 to 2990 mg/L also occurred.) In a similar incident reported in the same article, the local inhabitants of a community complained about a deterioration in taste of the local water and the widespread onset of diarrhea. Reportedly, the sulfate concentration had risen to 1348 mg/L in this location; unfortunately, the sulfate concentration before the increase was not given. The complaints disappeared when a new supply of water with a sulfate level of 210 mg/L was put into service.[15] Comparison of bacteriological indices before and after the outbreak suggested that the cause of the problem was not bacteria.[15]

Case Reports and Surveys

Human dose-response data for sulfate in drinking water are limited to a small number of case reports and two population surveys. The reports suggest that laxative problems can be expected when the sulfate reaches levels of several hundred milligrams per liter. The two population surveys also reported that no readily apparent chronic effects were attributable to sulfate in drinking water at levels up to about 1200 mg/L.

The doses and responses described below are from case reports and surveys of health effects attributed to drinking water with the concentrations of sulfate indicated:

- 650 mg/L promptly caused diarrhea in a 5-month-old infant.[14]
- 720 mg/L caused diarrhea in a 10-month-old infant and an unacclimated adult.[14]
- 1000 to 1200 mg/L in several public water supplies were consumed with no apparent "extensive physiological effects" and were "at least tolerable as drinking water."[7]
- 1150 mg/L caused an unacclimated 1-year-old child to develop persistent diarrhea within several days; unacclimated siblings and parents developed intermittent diarrhea 1 wk later.[14]
- A survey reports that "no diseases were traceable" to drinking water in which the total SO_4^{2} level remained below 1295 mg/L.[6]

The North Dakota State Department of Health conducted a survey that combined a mineral analysis of the water from 248 private wells and a questionnaire for the users of the wells. Among the questions asked was whether the water had a laxative effect on the users, especially on new users. Moore[7] tabulated these data (Table 2) to determine the probability that laxative effects will occur as a result of using water containing various ion-concentration ranges. The table shows a substantial jump in the probability that laxative effects will be reported when the sulfate or magnesium-plus-sulfate concentrations reach 1000 mg/L. The mean sulfate concentration in the 69 wells from which laxative effects were reported was 1250 mg/L (range: 14 to 5010 mg/L). The mean concentration in the 107 wells from which no laxative effects were reported was 500 mg/L (range: 0.0 to 2700). Overall, 25% of the respondents did not answer the question about laxative effects. The percentage of nonrespondents was highest among the wells with high ion content in the water, possibly because these wells were not used as sources of drinking water.[7]

Peterson[17] analyzed data from the same survey by plotting the yes and no responses to the question about laxative effects against the measured concentration of $MgSO_4$ and Na_2SO_4. To do this he selected about 300 pertinent questionnaires from the 2000 to 2500 collected by the state. From these data he concluded that water with over 750 mg/L of sulfate (from $MgSO_4$ and Na_2SO_4) is generally a laxative water, and that water with less than 600 mg/L of sulfate generally is not.[17]

Table 2. Comparison between total dissolved solids and ion concentration in water from wells, and reported laxative effects.[a]

Determination	Range (mg/L)	Number of wells in range	Laxative effects		Laxative effects not stated[b]	Percent of yes answers[c]
			Yes	No		
Total dissolved solids	0 to 1000	51	5	37	9	12
	1000 to 2000	72	12	45	15	21
	2000 to 3000	62	25	21	16	54
	3000 to 4000	30	13	11	6	54
	over 4000	33	14	4	15	78
Magnesium plus sulfate	0 to 200	51	9	34	8	21
	200 to 500	45	7	27	11	21
	500 to 1000	56	11	28	17	28
	1000 to 1500	36	18	10	8	64
	1500 to 2000	14	6	4	4	60
	2000 to 3000	21	13	3	5	81
	over 3000	14	5	1	8	83
Sulfate	0 to 200	56	10	36	10	22
	200 to 500	47	9	28	10	24
	500 to 1000	56	13	26	17	33
	1000 to 1500	34	16	10	8	62
	1500 to 2000	16	9	4	3	69
	2000 to 3000	20	9	3	8	75
	over 3000	8	3	0	5	100

[a] Table from Moore, 1952.[7]

[b] Column represents number of questionnaires in which the question about laxative effects was not answered.

[c] Percentage is based only on total yes and no answers. It is probable that most of the wells for which no statements were made were not regularly used as water supplies.

Mechanism of Laxative Effect

The modes of action of saline cathartics that result in laxative effects, which could adversely affect battlefield performance, are the retention of excess fluid in the intestinal lumen and increased motor activity in the intestinal tract (hyperperistalsis). Traditionally, this has been explained as poorly absorbed, but soluble, ions exerting an osmotic pressure that causes the retention of fluid in the intestinal lumen. This increase in bulk indirectly stimulates intestinal transit.[11] Other studies report that the cause of the

laxative effects of various saline solutions can be much more complicated. For example, in addition to osmotic effects, saline cathartics may increase the fluid volume of the intestinal tract by reducing water absorption in the small intestine and by stimulating substantial increases in the secretion of pancreatic, gastric, and intestinal fluids. It is not clear to what extent these effects are caused directly by the various ions of the saline cathartics or to what extent they are mediated by the cathartic-stimulated release of hormones, particularly cholecystokinin.[18,19] The same uncertainty exists in understanding how hyperperistalsis is induced.[18,19] Consequently, it appears that at least some of the saline cathartics have a fairly complex mode of action and can cause laxative effects by several different mechanisms.

CHRONIC EFFECTS

No anecdotal or case reports of adverse effects from chronic exposure to sulfates in drinking water were found, or are research efforts apparent that looked specifically for health effects attributable to long-term exposure to sulfates in drinking water. The two survey studies mentioned previously reported finding no evidence of obvious chronic effects.[6,7] After reviewing the available literature on the health effects of sulfate, the National Research Council Safe Drinking Water Committee concluded in 1977 that "no adverse health effects have been noted for concentrations of sulfate in drinking water less than about 500 mg/L," and they noted that diarrhea is the only physiological effect that has been documented at higher concentrations.[2]

ADVERSE EFFECTS ON PALATABILITY

It is widely accepted that sulfates can contribute to the undesirable taste of water with a high ion content; in fact, this taste consideration is the basis for most of the recommended standards for sulfates in drinking water.[2,16,20-23] The taste-threshold level generally is the level recommended as the maximum allowable concentration. However, as the U.S. Public Health Service points out, the taste-threshold level and the objectionable-taste levels may be very different.[16] The taste-threshold level actually may be the optimal level with respect to taste preference.[24,25] If one objective of a recommended standard is to prevent people from rejecting water because it has a bad taste, then the level at which people find the taste objectionable would be a more valid basis than taste threshold for a recommended-maximum-allowable concentration.

Because the objectionable level for sulfate, and probably most other ions, is well above the taste-threshold level, its adoption as the basis for a recommended standard could have the additional practical benefit of preventing unnecessary water treatment.

The ion levels that give water an objectionable taste appear to be influenced by several factors, making the measurement of objectionable-taste levels difficult. For example, acclimation appears to be an important factor influencing the sulfate levels at which people report an objectionable taste. Daily users of water high in sulfate (and other ions) apparently become accustomed to a taste that new or occasional consumers find close to intolerable.[16] Evidence that people adapt to the taste of water with high levels of sulfate comes primarily from reports of regular use of drinking-water supplies that have high sulfate concentrations. For example, water from a majority of 67 small supplies of public drinking water in South Dakota had sulfate levels of 1000 to 1200 mg/L. Also, there are reports of regularly used drinking-water supplies that have sulfate levels ranging from 2000 mg/L[26] up to 4400 mg/L.[5]

Studies involving taste panels or consumer surveys have been used to determine the levels of ions, including sulfate, that have an objectionable taste. For example, the mean rating from a panel that tasted water with 1000 mg/L and 2000 mg/L of $MgSO_4$ (i.e., sulfate concentration of 800 and 1600 mg/L, respectively) indicated that both concentrations could be accepted by a large portion of the panel as a daily drinking water even though the taste was not good.[27] Taste-panel studies evaluating the taste of equal concentrations of different ion combinations showed that all ions are not equal in their ability to degrade the taste of water.[27-29] The authors attributed the differences to the anions because all sulfate and bicarbonate solutions received mildly unfavorable ratings, all chloride solutions received moderately unfavorable ratings, and all carbonate solutions received strongly unfavorable ratings.[27,29] In another study, a panel evaluated the taste of water samples with sodium and different levels of chloride, carbonate, bicarbonate, and sulfate. From a multiple-regression analysis, those researchers found that the taste ratings could be described by a first-degree function with no interaction term. As a result, they concluded that, at least under the conditions of their study, no important synergistic or masking effects occurred between the ions.[29] Their ranking of sulfate as one of the weakest anions with respect to its ability to elicit a taste sensation is consistent with the findings of three other studies.[25,30,31]

In another set of studies, a taste panel in the Netherlands also rated the taste quality of a series of salt solutions.[25] In contrast to the studies discussed previously, the authors of the Netherlands study concluded that cation effects dominated the taste ratings. However, their conclusion that sulfate had the weakest effect among the anions was similar to the findings previously discussed. Another contradicting conclusion was that sulfate had a strong masking effect on magnesium. The taste panel gave the sulfate

solutions mean ratings of objectionable (i.e., 50% of the panel found the water objectionable or worse) at $MgSO_4$ concentrations of 840 mg/L and at $CaSO_4$ concentrations in excess of 1020 mg/L. The reasons for the different findings of the two research programs may be attributed, at least in part, to the use of different test methods (including a different rating scale), different taste panels, and different ion concentrations for taste evaluation.[25]

Table 3 lists the taste thresholds that have been reported for a variety of sulfate salts. The wide range of detection levels, extending over two orders of magnitude, can be explained partly by the use of different tasting procedures and differences between taste panels. For example, in the study that measured the lower of the two levels listed for detection of Na_2SO_4 in Table 3, taste-panel members were selected for their sensitivity to detecting NaCl. However, it is apparent also that the associated cation can substantially affect the detection level of a sulfate salt. Cox et al.[24] noticed this effect when comparing the detection levels of various sodium salts. These researchers concluded that neither sulfate nor any of the other anions tested (Cl^-, F^-, and PO_4^{-3}) stimulated the threshold-recognition apparatus, or else the effect was masked by the stronger effect of the sodium.[24]

Table 3. Range of sulfate-salt concentrations in drinking water detected by different taste panels.

Salt	Concentration detected (mg/L)				Reference
	Median		Range		
	Salt	Anion	Salt	Anion	
Na_2SO_4 [a]	126	85	18 to 284	12 to 192	24
Na_2SO_4	350	237	250 to 550	169 to 372	32
$CaSO_4$	525	370	250 to 900	177 to 635	32
$MgSO_4$	525	419	400 to 600	320 to 479	32
$MgSO_4$	500	400	--	--	33
$FeSO_4$	5	3	0.5 to 10	0.3 to 6	32
$Al_2(SO_4)_3$	75	63	25 to 200	16 to 130	32
$CuSO_4$	15	9	5 to 25	3 to 15	32

[a] Panel selected for sensitivity to detecting NaCl.

Another point is important regarding sulfate and water palatability. Under anaerobic conditions, sulfate can be biochemically converted to sulfide and then to hydrogen sulfide.[1] This conversion can create a serious odor problem.

DEVELOPMENT OF RECOMMENDATIONS FOR STANDARDS

Major uncertainties exist in the method for calculating the recommended standard for sulfate. In addition, assumptions were required to bridge gaps in the current knowledge about the health effects of sulfate.

METHOD AND RATIONALE

Based on the previous discussion of health effects associated with sulfate, and assuming a 15-L/d consumption rate for drinking water, it appears that the laxative effects of sulfate threaten performance degradation at fairly low concentrations. Because no chronic effects have been reported from sulfate in drinking water, it is suggested that a long-term (1-y) standard for sulfate is not necessary. To prevent laxative effects caused by the ingestion of sulfate ions in 15 L of water, a maximum sulfate concentration of 100 mg/L is recommended. At a daily water-consumption rate of 5 L/d, a maximum sulfate concentration of 300 mg/L is recommended. Sulfate ions do not appear to give water an objectionable taste at this level. However, it should be noted that an objectionable taste may still be apparent if one of the cations less commonly associated with sulfate, but having a strong taste (e.g., Fe^{+2}), is present. The maximum recommended concentration of 100 mg/L is the concentration that results if the assumed laxative dose (1490 mg) of sulfate ions is dissolved in a volume of water constituting the assumed daily water-consumption rate of 15 L/person. Similarly, the maximum recommended concentration of 300 mg/L is the concentration that results if the same dose of 1490 mg is dissolved in a volume of water constituting the assumed daily water-consumption rate of 5 L/person.

CALCULATION OF RECOMMENDATIONS FOR STANDARDS

The calculations for assumed water-consumption rates of 15 and 5 L/d are shown below. The calculation for a 5 L/d water-consumption rate is included because, under less severe conditions, 5 L is a more reasonable amount of water to expect military personnel

to drink in 1 d. In addition, this allows comparison with other military drinking-water standards, which assume a daily water-consumption rate of 5 L.

$$\frac{1490 \text{ mg/d}}{15 \text{ L/d}} \approx 100 \text{ mg/L} .$$

$$\frac{1490 \text{ mg/d}}{5 \text{ L/d}} \approx 300 \text{ mg/L} .$$

MAJOR UNCERTAINTIES AND ASSUMPTIONS

The most important uncertainties in this calculation are (1) those associated with the choice of 1490 mg as the maximum allowable dose of sulfate ions that a person can ingest each day without suffering adverse health effects, (2) those associated with extrapolating from a single dose of 1490 mg to multiple doses that total 1490 mg, and (3) those associated with the laxative properties of other solutes in the water. Other assumptions included in the calculation are the water-consumption rates of 15 L/d and 5 L/d, which are considered to be reasonable maximum and minimum levels for military field personnel. The recommended standards may be conservative because we cannot directly account for the effect of accumulated individual doses of sulfate that would total a toxic dose. For example, a laxative administered clinically would be given in a single dose; however, a laxative dose of sulfate consumed in repetitive drinks of water over the course of a day may not exert the same response because of elimination from the gastrointestinal tract. Further research is needed to resolve this uncertainty, and until the results of such research are available we assume that a cumulative laxative dose will be as effective as a single laxative dose.

Maximum Allowable Dose

A single dose of 5 g of epsom salts ($MgSO_4 \cdot 7H_2O$) or Glauber's salt ($Na_2SO_4 \cdot 10H_2O$) contains 1950 mg or 1490 mg of sulfate ions, respectively. Both doses are sufficient to produce a "significant laxative effect" in fasting individuals.[11] To attribute the laxative effect to sulfate ions alone, one must assume that the cation has no laxative properties. Because magnesium and other poorly absorbed ions are believed to cause laxative effects, the assumption is better for Glauber's salt, in which the cation is readily absorbed sodium. Thus, 1490 mg of sulfate ion appears to be sufficient to cause a "significant laxative effect" in a fasting individual. However, it must be noted that

quantitative dose-response data are sparse for the laxative effects of sulfate, or any other ions. Thus, some uncertainty exists about the magnitude of the response to be expected from a 1490-mg dose of sulfate ions.

Another important uncertainty related to choosing the maximum allowable dose is the presence of tolerant or sensitive subpopulations. As discussed previously, individuals apparently can develop a tolerance for water that is high in sulfates. In this assessment, however, we are trying to determine quantitatively a sulfate level that will protect individuals who have not developed a sulfate tolerance. As implied previously, individuals will be more sensitive to the laxative effects of sulfate salts if they have empty stomachs.[34,35] Moreover, a fairly wide range of responses is apparent among individuals in a given nutritional status.[35-38]

A study by Bouchier et al.[35] indicates the magnitude of the effect that fasting has on the laxative response. In this study, 10 g of magnesium sulfate (not specified as the hydrated salt) were given to patients with normally functioning ileostomies. Response was measured as the amount of discharge from the small intestine. The mean discharge nearly doubled in nonfasting individuals and nearly tripled in fasting subjects. The increased discharge primarily resulted from an increase in the water content. Presumably, the colon (of individuals without ileostomies) would normally absorb at least some of this water. How this retention of water in the intestines would affect the water balance of soldiers requiring 15 L/d of water is not clear.

Single-Dose to Multiple-Dose Extrapolation

By diluting the one-time 1490-mg dose of sulfate in the volume of water consumed during one day we assume that either the ions themselves or the laxative effect of the ions will accumulate over a day's time. A check on the validity of this assumption can be made by comparing a laxative concentration, calculated in this manner, with concentrations at which laxative effects have been reported. For example, the combination of a sulfate-ion concentration of 745 mg/L with a normal 2-L/d water-consumption rate would give an individual the laxative dose of 1490 mg of sulfate ions. This finding correlates closely with those levels reported in the literature to cause laxative effects (Table 4) and therefore indicates that the assumption concerning daily accumulation is reasonable. Above the levels reported by Peterson[17] (750 mg/L) and Moore[7] (1000 mg/L), a substantial increase occurred in the number of reports of laxative effects. However, below these levels, 25%[17] and 33%[7] of the respondents still reported that their water had laxative effects. Whereas some of these cases may represent

Table 4. Sulfate levels in drinking water associated with increased incidence of laxative effects.

Laxative concentration (mg/L)	Type of data	Reference
720	Case report	17
≥ 750	Survey	15
≥ 1000	Survey	5

individuals who were especially sensitive to sulfate ions, it is more likely that other causative factors, such as other laxative-producing ions (e.g., Mg^{+2}) or waterborne microbes were responsible.

Another important uncertainty is whether the assumption of accumulation will still be reasonable at a 15-L/d water-consumption rate. One study, in which segments of the small intestine were perfused with saline solutions, showed that the strength of response of the components of laxation (e.g. water absorption, fluid secretion) are related to the concentration of the salts within the intestinal lumen.[19] It has also been shown that some laxatives act by diminishing the ability of the intestinal mucosa to absorb water from the intestinal lumen.[39] Therefore, it is conceivable that a 15-L/d water-consumption rate could dilute the ions, causing laxative effects to a point below which any significant laxative effect would be apparent. However, it is also possible that the sulfate ions would diminish the water-absorbing ability of the intestinal mucosa and that a large volume of water would collect in the intestines. The resulting distention would induce intestinal motility and result in a more severe laxative response at a 15-L/d consumption rate than at a 2-L/d rate.

Thus, it appears that at levels of sulfate ingestion in excess of about 1500 mg/d, a large increase will occur in the number of fed (nonfasting), unacclimated people reporting laxative effects.

Effects of Other Solutes

The effect of other solutes in the water, in addition to sulfate, is an important uncertainty in predicting the laxative potency of water with a high sulfate concentration. This is because other solutes in the water will also contribute to the osmotic pressure inside the gut and because other ions may induce laxation by physiological mechanisms.

Table 5. Comparison of recommended standards for sulfate in drinking water.

Recommended standard (mg/L)	Assumed water-consumption rate (L/d)	Source
100	15	Maximum concentration recommended by this study
300	5	Maximum concentration recommended by this study
200[a]	2.5	WHO, International Standards; 1971[22]
250	2	U.S. Public Health Service; 1962[16]
250[b]	2	U.S. EPA, Secondary Drinking Water Standards; 1979[20]
250[c]	2.5	WHO, European Standards; 1970[21]
400[d]	2.5	WHO, International Standards; 1971[22]
400[e]	—[f]	TB MED-229; 1975[40]
400[e]	5	QSTAG-245; 1985[41]
500[g]	2	California Water Resources Control Board; 1963[3]

[a] "Highest desirable level."

[b] "Recommended limit," no mandatory limit proposed.

[c] "Approximate level, above which trouble may arise."

[d] "Maximum permissible level."

[e] Minimum treatment requirement for assuring potability for long-term consumption (>7 d).

[f] Assumed consumption rate for calculating a recommended standard is not specified.

[g] "Will not be detrimental" for domestic water supply.

Thus, the laxative effects of a high-sulfate water are likely to be supplemented by solutes other than sulfate ions, and they are difficult to predict.

RECOMMENDATIONS FOR STANDARDS

Table 5 compares the recommended standards from this study with those proposed by several other agencies. Based on our assessment of the available data base, we recommend that the standard for sulfate in military field drinking-water supplies be set at 100 mg/L for a 15-L/d water-consumption rate and 300 mg/L for a 5-L/d water-consumption rate. The 100 mg/L level from this study is the lowest allowable

concentration recommended because it assumes a 15 L/d water-consumption rate; however, it represents a daily dose of 1500 mg. The standard recommended here for a 5-L/d water-consumption rate is 25% below the comparable minimum treatment requirement stated in the latest edition of QSTAG-245.[41]

The recommended standards at 200 and 250 mg/L in Table 5 are based on concern about taste, specifically the taste threshold of sulfates. The recommendations at 400 and 500 mg/L made by the World Health Organization (WHO)[21] and contained in the publication of the California State Water Resources Control Board,[3] are intended to prevent any physiological effects, including gastrointestinal irritation and laxation. Although not stated, the higher recommendations contained in the publication by the California State Water Resources Control Board[3] and a 1971 WHO[22] report appear to include a safety factor, which these authors applied to the same dose-response data cited in this document.

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CHAPTER 7. ARSENIC

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ABSTRACT

The purpose of this chapter is to develop criteria and recommend military drinking-water standards for inorganic arsenic. The recommended standards are intended to prevent performance degradation or irreversible effects in troops who will be exposed to water that contains arsenic for up to 7 d or up to 1 y. Based on human no-effect levels, 7-d and 1-y standards are calculated assuming both a 15-L/d and a 5-L/d water-consumption rate. Uncertainties and assumptions in the standards are identified and explained to allow maximum flexibility in administration. For an assumed daily water consumption of 15 L, the recommended standards are 100 μg/L for a period up to 7 d and 20 μg/L for a period up to 1 y. For an assumed daily water consumption of 5 L, the recommended standards are 300 μg/L for a period up to 7 d and 60 μg/L for a period up to 1 y.

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INTRODUCTION

The purpose of this research is to recommend the maximum concentrations of arsenic that can be tolerated in drinking water without causing performance degradation or irreversible effects in military personnel. Different maximum concentrations are recommended for assumed exposure periods up to 1 wk (7 d) and up to 1 y. Under each assumed exposure period, two maximum concentrations for inorganic arsenic are recommended: one based on the consumption of 15 L/d of water and the other for consumption of 5 L/d. Water-consumption studies of men performing physical labor in hot climates and U.S. Army field experience in desert situations indicate that 15 L is not an unreasonable amount of water to expect individuals to drink in a day. Five liters is a more reasonable expectation under less severe conditions.

This chapter describes some of the chemical properties of arsenic that affect its toxicity and the likelihood of its presence at toxic levels in drinking water. We briefly describe some of the most common and field-practical methods for measuring arsenic levels in water. The pharmacokinetic (i.e. absorption, distribution, metabolism, and elimination) characteristics of arsenic in humans are included to explain (1) why animal studies are a poor base from which to predict the human health effects of arsenic, (2) why different forms of arsenic have different toxicities, and (3) why different epidemiology studies show different health effects in the people exposed to arsenic. We also include a brief summary of the effects that arsenic has produced in people following subacute and chronic exposures. The highest exposures in these studies that presumably would not cause any performance degradation are the basis for the recommended standards. We then describe how the recommended standards were calculated, and we make explicit the important assumptions that are incorporated in the recommendations.

GENERAL PROPERTIES

Arsenic (As) is a semimetallic element in Group 5A (N, P, As, Sb, Bi) of the Periodic Table.[1] It is capable of forming numerous different organic and inorganic compounds,[2] many of which can potentially be found in water. To understand the toxic effects of arsenic in drinking water, two chemical properties are of special importance. These properties are the oxidation state of arsenic and the water solubilities of the various arsenic compounds. The oxidation state is important because the toxicity of arsenic varies between the different states. Solubility is important because it affects the likelihood that an arsenic compound will be present in water. It is also important because it affects the extent to which an arsenic compound is absorbed from the gut.[3]

Arsenic is stable in four valence states (+V, +III, 0, and -III) under oxidation conditions that can be found in water; but elemental arsenic, As(0), occurs only rarely, and As(-III) is stable only under extreme reducing conditions (low Eh).[4] Thus, because As(+III) and As(+V) are the most thermodynamically stable states under the pH and Eh conditions of most natural waters, they are the oxidation states actually found when analyzing waters that contain arsenic.[4] In oxygenated waters (high Eh values) As(V)* is more stable than As(III), but a large fraction of the total arsenic may still be present as As(III) because the rate of oxidation to As(V) is slow at neutral pH values.[4] Measurable conversion of As(III) to As(V) occurs on the order of days to months in seawater.[5] Clement and Faust tracked the oxidation of 0.368 mg/L of arsenite (III) to arsenate (V) following the aeration of an anaerobic sample of natural water in their laboratory; they observed complete conversion in 6 d.[6]

The most common forms of arsenic found in natural water are inorganic arsenate [As(V)] and arsenite [As(III)]. In oxygenated waters, arsenic acid (As(V)) species ($H_3AsO_4^-$, $H_2AsO_4^-$, $HAsO_4^{-2}$, and AsO_4^{-3}) are stable; under mildly reducing conditions, the arsenious acid (As(III)) species (H_3AsO_3, $H_2AsO_3^-$, and $HAsO_3^{-2}$) become stable.[4] Other forms of inorganic arsenic that can exist in natural waters are arsenic oxides, arsine, arsenic halides, and arsenic sulfides. Arsenic trioxide (As_4O_6) in water results in solutions of arsenious acid,[7] and arsenic pentoxide (As_2O_5) slowly dissolves in water to form arsenic acid.[8] As previously mentioned, arsine, where arsenic is in the -III state, is not stable under the pH and oxygenation conditions of most natural waters. In addition, arsines (arsine and alkylated arsine compounds) are quite volatile.[8] Arsenic halides are also unstable in water because they are rapidly hydrolyzed and are rather volatile.[7] The arsenic sulfides are either insoluble or only slightly soluble in water.[7] The most water-soluble arsenic sulfide listed in the Handbook of Chemistry and Physics[9] is As_2S_5, which will dissolve to the extent of 1.36 mg/L in water at 0°C.

In addition to the inorganic forms of arsenic, several organic forms can exist in water; these include methylarsines, alkylchloroarsines, methylarsenic acids, and many other more complex compounds. It has already been mentioned that arsines are not thermodynamically stable in most natural waters, and at least the methylarsines are volatile and poorly water-soluble.[4,8] The alkylchloroarsines are reasonably stable with respect to hydrolysis but are quite reactive with reduced sulfur compounds.[10] The methylated arsinic acids--methylarsonic acid and dimethylarsinic acid (cacodylic

* Roman numerals without a "+" or "-" in front are to be interpreted as "+" unless otherwise specified (e.g., As(III) = As(+III), and As(V) = As(+V)).

acid)--are both water-soluble; dimethylarsinic acid is extremely stable.[8] It is also possible that other organic arsenic compounds can be present in water, but very little is known about their reactions in water environments.[11]

OCCURRENCE

Arsenic can be present in a wide variety of natural waters, as is illustrated in Table 1. Typically, the levels are well below levels of concern for health effects. For example, Durum et al.[12] found that 79% of 727 water samples taken from U.S. rivers and lakes had less than 10 µg/L of total arsenic; only 2% had levels exceeding 50 µg/L. Results of seawater analyses indicate that typically it has only low total arsenic levels as well.[13] However, very high levels of arsenic can be present in water, and the total arsenic levels shown in Table 1 are the highest total arsenic levels reported for the various types of waters. These high concentrations represent levels that could challenge field treatment equipment.

Studies that have looked for arsenic in natural waters have found that inorganic arsenate and arsenite are normally the predominant forms and that methylarsonic acid (MAA) and dimethylarsinic acid (DMAA) can be present at detectable levels but represent a small fraction of the total arsenic found. For example, Braman and Foreback looked at arsenate (V), arsenite (III), MAA, and DMAA in seven fresh waters with low levels of total arsenic (0.25 to 3.58 µg/L) and three saline waters with total arsenic levels ranging from 1.48 to 2.28 µg/L.[22] Expressed as the percentage of total As detected in the fresh waters, As(V) ranged from 11.4 to 100%, As(III) from <2 to 76.5%, DMAA from <0.02 to 0.62%, and MAA from <0.02 to 0.22%. The highest levels of the methylated arsenic were found in small lakes and ponds and the lowest in moving streams.[22] In saline waters, As(V) represented 23.6 to 81.9% of the total arsenic whereas As(III) ranged from 4 to 27%. The methylated forms were again a very small fraction; DMAA ranged from 0.20 to 1.00% and MAA from <0.02 to 0.08% of the total arsenic detected.[22] In three other studies, researchers also looked for the presence of organic forms of arsenic in waters with elevated total arsenic levels. They found only inorganic arsenate and arsenite.[23-25] The analyses by Irgolic[25] are particularly important because these were done on water samples from areas where people had suffered health effects attributed to arsenic in their drinking water. The failure to find organic arsenic compounds in these waters supports the conclusion that the observed effects were caused by arenate and arsenite and were not due to other arsenic compounds.[25]

Table 1. Reported arsenic concentrations in several waters.

Total arsenic level found (µg/L)	Description of water	Reference
<10	Surface water in unpolluted areas, U.S.A.	12
1 to 8	Seawater	13
10 (ev)	Oil-field waters	14
1.1 to 54.5	Lake waters, Greece	15
800	River water, Chile; natural sources	16
1,100	River water, South Carolina; industrial contamination	12
≤ 3,000	Well water, Japan; industrial contamination	17
8,500	Thermal water, New Zealand	18
11,800 to 21,000	Well water, USA; pesticide burial in 1930s	19
0.2 to 40,000	Hot springs	14
125,000	Well water, Malaysia; pesticide contamination	20
≤ 243,000	Brines, e.g., Searles Lake, California	21
3 to 400,000	Ground and mine water near arsenic-rich deposits	14

Aware of the importance of the arsenate/arsenite [As(V)/As(III)] ratio, several people researched these species and reported findings from several different waters. Clement and Faust reported that arsenite can be 100% of the inorganic arsenic present in an anaerobic reservoir water.[6] The arsenic in a New Zealand geothermal water was reported to be 90% arsenite.[10] Johnson[26] noted that the arsenite/arsenate ratios reported for seawater ranged from 10^{-1} to 10^{1}. In several reports on ground water, arsenite comprised from <1% to 77% of total inorganic arsenic, but most reported values were in the range of 30 to 50%.[6,23-25,27] Samples from a well-aerated stream had 7 to 8% of total arsenic as As(III).[6]

Arsenic can enter the water as the result of a variety of natural processes and human activities. Most waters that contain arsenic appear to have dissolved it from arsenic-bearing minerals in natural aquifers or mine tailings. Arsenic compounds are also used in many pesticides and herbicides (e.g., Agent Blue).[10] Manufactured products that use such compounds include glass, metals, industrial chemicals, pharmaceuticals, and electronics.[2,10,28,29]

METHODS FOR DETECTION OF ARSENIC

Total arsenic measurement generally involves a first step of reducing arsenic to arsine by zinc in an acid solution. In the Army method for arsenic measurement, detection is made by the observation of color change on paper strips impregnated with mercuric bromide.[30,31] This procedure can detect amounts as small as 1 μg of total arsenic.[30] More precise and accurate methods of detection involve reacting the arsine with silver diethyldithiocarbamate and measuring the color change with a spectrophotometer,[30] and producing a fluorescent enzymatic reaction involving inorganic arsenic and then analyzing the resulting fluorescence emission with a spectrofluorometer.[32] These and many of the other methods for measuring arsenic in water (e.g., atomic absorption spectrophotometry) would, however, require equipment not normally available during field operations.

PHARMACOKINETICS

Pharmacokinetic processes are an important influence in determining the toxic response to any chemical. Arsenic is thought to be absorbed from the gastrointestinal tract, distributed in the body, metabolized (detoxified), and eliminated. Comparisons have been made with similar processes in a few animals, and they help to illustrate why animals are poor models for extrapolation of dose-response data for arsenic. In addition, some factors alter the pharmacokinetics of arsenic and this may explain, therefore, some of the variability we have found in response to arsenic in epidemiology studies.

ABSORPTION

Work by Crecelius,[33] Bettley and O'Shea,[34] and Coulson et al.[35] suggests that a large fraction of soluble inorganic arsenic is absorbed from the gut in humans. Following administration of soluble arsenite, Bettley and O'Shea and Coulson et al. found less than 5% of the administered dose in feces. Presumably, >95% of the administered dose was absorbed. Crecelius analyzed urine after administering arsenite in wine and found that about 80% of the dose was excreted in the urine, suggesting that a significant fraction had been absorbed; elimination via urine occurs generally following gastrointestinal absorption. In another experiment, Crecelius found only 50% of the arsenic administered as an arsenate-rich well water when he analyzed the urine (low recovery of administered dose).[33]

Factors that can affect the extent of absorption include the physical properties and chemical forms of the arsenic species and the presence of arsenic-complexing compounds in the intestines. For example, if arsenic is administered in an insoluble matrix and is not available for absorption, the toxic effect may be delayed or may not be seen at all.[36] In an experiment on himself, Mappes could not detect any increase in urinary arsenic after taking 12 mg of insoluble arsenic selenide,[37] suggesting no absorption from the intestines. In studies on rats, Nozaki et al. found that intestinal absorption of arsenite (As_2O_3) was inhibited by casein or its enzymatic hydrolysis products, polypeptides, and phosphoric acid.[38] This last point is significant because some of the epidemiology studies performed on arsenic-affected populations (e.g., Taiwan and Chile) indicated that the people in these areas had low-protein diets,[39] and poor nutrition was speculated to be a factor contributing to the appearance of chronic arsenic poisoning.[40]

DISTRIBUTION

The body of an adult human normally contains approximately 20 mg of arsenic.[36] Thus, at a concentration of 0.2 to 0.3 mg/kg, arsenic is the 12th most abundant element in the body, comparable to Mn, Ba, and I.[21] Arsenic has been found in virtually all tissues and organs of the human body. Reports vary as tc which organs accumulate the highest levels, but substantial amounts are generally reported in the heart, lung, kidney, liver, skin, and brain.[21,41-47] The presence of arsenic in the central nervous system shows that it can penetrate the blood-brain barrier, and a study of the distribution of arsenic in the brain suggests that arsenic preferentially accumulates in the higher lipid-content components of nerve tissue.[46]

Yamauchi and Yamamura measured the levels of different arsenic species in human tissues and organs.[41] They found As(III) and As(V) in all tissues, but As(V) accounted for about 72% of total arsenic whereas As(III) accounted for about 20%. Dimethylarsinic acid (DMAA) was nearly as ubiquitous as the two inorganic species, but it was present at a lower level, accounting for about 10% of total arsenic in the tissues where it was found. No DMAA was detectable in the cerebellum or cerebrum. The fourth species of arsenic found in the tissues was MAA. It accounted for about 3% of the total arsenic in the liver and 4.6% in the kidney, the only organs where MAA was detected. No trimethylarsenic acid [sic] was detected in any of the samples.[41] Thus, it appears from Yamauchi and Yamamura's study that it is the two inorganic arsenic species that are the most prevalent in tissues; although the ratios of the mean As(III) to As(V) levels in the various tissues varied somewhat (0.18 to 0.37), it is As(V) that is found at the highest levels in all tissues.

At least in animals, evidence suggests that the distribution and retention of arsenic in the body can vary with the size of the dose, the length of time following administration, the species of arsenic administered, and the duration of administration.[36,48]

METABOLISM

The metabolism of inorganic arsenic in humans is not yet fully understood but appears to include the oxidation of arsenite to arsenate, followed by the formation of less toxic methylated arsenic species. These steps may not be the same in humans as in laboratory animals. In addition, factors such as the contemporaneous presence of other metals in the body appear capable of substantially affecting arsenic metabolism in animals.

Following the ingestion of inorganic arsenic (both arsenite and arsenate) solutions by humans, the arsenic forms that appear in the urine are DMAA, mono-MAA, and inorganic arsenate and arsenite.[22,33,49,50] The most abundant metabolite is DMAA, accounting for one-half to two-thirds of the total arsenic found in the urine. The metabolite MAA accounts for less, but is still a substantial (8 to 21%) portion of the urinary arsenic. The remaining arsenic is inorganic arsenite and arsenate. The ability to detect the methylated metabolites at low levels is a fairly recent advance in analytical methods, and so far the monomethyl metabolite has been detected only in humans.[10] If it is not found in animals in future studies, an explanation of the difference in the chronic effects of arsenic in animals and humans may be possible.[50]

Oxidation of inorganic arsenite to inorganic arsenate also appears to be a biotransformation that arsenic can undergo in humans.[45,49] For example, Mealey et al. injected trivalent ^{74}As into humans and recovered the ^{74}As in urine as a mixture of arsenite and arsenate, with arsenate being the predominant form.[45] Ginsburg found that arsenate in dogs could, in part, be reduced to the more toxic arsenite.[51] Whether this happens in humans or other animals has not been demonstrated.[52]

Because the inorganic arsenate and the two methylated metabolites, DMAA and MAA, are generally less toxic than the inorganic arsenite; the oxidation of arsenite to arsenate and the methylation step can be considered detoxification processes. Another factor that can alter the toxicity of arsenic is the presence of metals that have antagonistic or synergistic effects on the toxic effects of arsenic. This has not been well studied in humans, but animal studies have shown that selenium can protect against the effects of arsenic, and vice versa.[10] Cadmium and lead may exacerbate the effects of arsenic.[10] A better understanding of the relationship between these or other agents and arsenic may help explain some of the apparent inconsistencies in the epidemiology of arsenic.

The use of arsanilic acid (pentavalent) as a diet supplement improves the growth rate of poultry, hogs, and cattle.[21] Rats that were fed a diet containing 30 μg/kg of arsenic developed a rough coat and exhibited a significantly lower growth rate than did a control group. The control-group diet was supplemented with 4.0 ppm of arsenate and 0.5 ppm of arsenite.[53] Schroeder and Balassa[21] did not observe any signs of nutritional deficiency in a group of rats that were fed a diet containing only 53 μg/kg. Arsenic is not known to be a constituent of any critical molecule of the body.[54] Though it is not a widely accepted fact, some researchers believe that arsenic is an essential nutrient.[55-57]

ELIMINATION

Essentially all arsenic is eliminated from the body by excretion through the kidneys. A large fraction of absorbed inorganic arsenic appears in the urine within a few days, and a very small fraction may be found in the feces as a result of arsenic in biliary excretion or other gastrointestinal fluids. In addition, very small amounts of arsenic may be eliminated in sweat, milk, hair, or exfoliating skin. Despite rapid elimination of the bulk of absorbed arsenic by the kidneys, a small fraction is eliminated more slowly. The accumulation of this slowly eliminated portion probably causes the chronic health effects associated with arsenic. Therefore, ingestion of inorganic arsenic over a long period of time should be kept at low levels to prevent the accumulation of sufficient arsenic to cause performance degradation or irreversible effects.

Several studies have measured the arsenic levels in urine, following a single administration of inorganic arsenic to human subjects. The studies show that the bulk of the absorbed dose is normally eliminated in urine within a few days. For example, Yamauchi and Yamamura[58] administered to a 70-kg male subject an oral dose of 0.70 mg of As(III) as a solution of As_2O_3. Within 12 h, 40% of the dose appeared in the urine; 70% appeared within 72 h. Crecelius[33] gave an arsenite-rich (0.050 mg As(III) and 0.013 mg As(V)) wine to a 70-kg male adult and was able to recover 80% of the administered total arsenic from the urine within 61 h. Following the oral administration of 1.0 mg of arsenic as As_2O_3 to two healthy male adults, Coulson et al.[35] recovered about 73 and 103% [sic] of the dose from the urine of the two subjects within 7 d.

In two studies higher doses of trivalent arsenic as As_2O_3 were administered to human adult volunteers. In one of these studies, Bettley and O'Shea[34] gave a total of 8.52 mg, in three equal doses (i.e., 2.84 mg/dose) at 8-h intervals, to three healthy males. By the end of the 10th day, arsenic recovery in the urine amounted to 48.2, 52.0, and 56.1% of the administered dose. In the second study, Hunter et al.[43] gave four

subcutaneous injections at a higher dose, 1.5 mg of ^{74}As as As_2O_3, to two healthy male volunteers on each of four consecutive days. By the 10th day after the first injection, 40% and 52% of the ^{74}As had been eliminated in the urine. In another study, ^{74}As was injected intravenously to five subjects with normal renal function, at a dosage of 2.3 mCi/70 kg. More than 90% of the arsenic was As(III), with As(V) constituting only a small fraction of the total arsenic. At the end of 1 h, total arsenic recoveries ranged from 18 to 30% of the injected dose; at the end of 4 h, recovery ranged from 36 to 58%; and at the end of the 9th day recovery ranged from 57 to 90%. One of the subjects was observed for 18 d, and at the end of that period, 96.6% of the injected dose was recovered in the urine.

In addition to the studies in which inorganic arsenic was administered predominantly or entirely in the trivalent state, two studies were made with pentavalent inorganic arsenic. Human volunteers were given low doses and their urine elimination was monitored. In one of these studies, Tam et al.[50] gave oral doses (~1.0×10^{-5} mg) of ^{74}As to six adult males. On the first day after dosing, 22.4% of the dose appeared in the urine; within the first 5 d, 58% was detected. Pomroy et al.[59] also gave a small dose (6×10^{-8} mg) of ^{74}As as arsenic acid to six male volunteers. At the end of 7 d, 62% of the dose had been recovered in the urine. Although biliary excretion of arsenic occurs in several animal species, no studies to date have established whether it also occurs in humans. In a few studies, arsenic was found in the feces, following oral or parenteral administration of inorganic arsenic. For example, Coulson et al.[35] recovered 1.9 and 3.1% of an orally administered dose of arsenite in the feces of two subjects. Pomroy et al.[59] recovered an average of 6.0% (range 3.5 to 10.9%) of an orally administered dose of arsenate that had been administered in a gelatin capsule to six subjects. In both cases, the presence of arsenic could also be attributed to less than complete absorption. Following the injection of arsenite into human volunteers, Mealey et al.[45] found 0.21% of the injected dose in the feces of one subject within a week, and 1.30% of the dose in the feces of the other subject within 17 d. Hunter et al.[43] recovered 0.04 and 0.02% of the injected arsenite in the feces of two subjects within 10 d from the beginning of injections, which were given on four consecutive days. These studies do not establish the existence of a biliary route of excretion for absorbed arsenic; but the possibility that it may exist cannot be dismissed. The low recoveries of arsenic from the feces suggest that if biliary excretion does exist for arsenic, it is not a route by which a large fraction of arsenic is eliminated from the body.

Other routes of arsenic elimination exist as well, but they account for a very small amount, even when considered together. One route of particular importance in a desert climate is sweat. The World Health Organization (WHO) reported that Vellar measured an average arsenic concentration of 1.5 μg/L in the sweat of two human subjects.[10] Under

hot, humid conditions, the loss was 2 μg/h. Arsenic was not detected in the sweat of one of the human subjects in the study by Pomroy et al.,[59] in which subjects were given the very low dose of 0.06 ng. The other subjects in the Pomroy et al. study were not tested for this route of elimination.

Because arsenic is deposited in the hair, skin, and nails, these depositions can be viewed as routes of elimination. After a population was exposed to about 3 mg of arsenic in soy sauce, a report by the WHO estimated the maximum fraction of the ingested dose that was eliminated by the hair was 0.6%.[10] Elimination of arsenic by the normal loss of superficial skin cells (desquamation) was measured in 10 people who apparently had not been exposed to abnormal levels of arsenic.[60] The daily arsenic loss was 0.1 to 0.2 μg/24 h.[60] Grimanis et al. measured arsenic levels of about 3 μg/L (range 0.6 to 6.3 μg/L) in human milk, and they confirmed that such milk can also be a route of arsenic elimination.[61]

Despite the fact that the kidneys rapidly begin to remove the bulk of absorbed arsenic from the body, a small portion is eliminated at a slow rate. If even relatively small doses are repeated, this small fraction could accumulate to a level sufficient to produce adverse, chronic health effects. For example, Mealey et al.[45] looked for arsenic in the muscle, liver, and kidneys of a subject 10 wk after an injected dose of predominantly arsenite (>90%). At that time, over 4% of the originally administered dose could still be detected. Mealey et al. also found that a three-compartment kinetic model could be used to represent the distribution and elimination in their human subjects. Equilibration of the third compartment appeared to be complete by the 6th day after injection and probably represented the elimination of the small residual arsenic pool. The elimination rate from this compartment was estimated to be about 0.3% of the residual arsenic per hour.[45] Pomroy et al. also found that a three-compartment model best represented elimination of inorganic arsenic. In their models, 65.9% of the arsenic had a half-life of 2.09 d, 30.4% had a half-life of 9.5 d, and 3.7% had a half-life of 38.4 d.[59]

HEALTH EFFECTS

The health effects associated with the ingestion of inorganic arsenic depend on the form of inorganic arsenic, particularly the solubility of the arsenic species and the valence of the arsenic atom. This probably results from differences in the absorbability and the mechanism of action of different arsenic species. Most studies on the health effects of inorganic arsenic involve exposure to incompletely characterized mixtures of arsenic species. In addition, recent epidemiology literature on inorganic arsenic identifies a level of total inorganic arsenic that would not cause performance degradation in soldiers.

VARIATION OF HEALTH EFFECTS WITH FORM OF INORGANIC ARSENIC

Human health effects that occur following the ingestion of inorganic arsenic are varied, even at comparable doses. It is probable that at least part of this difference results from differences in the toxic properties of the various forms of inorganic arsenic. The most important characteristics are the water solubility of the arsenic compound and the valence of the arsenic itself.

Done and Peart[3] examined reports of arsenic poisoning and compared the fatality incidences resulting from relatively water-soluble and water-insoluble arsenicals. The average mortality rate (deaths/incidents) for the soluble compounds--sodium arsenite, sodium arsenate, and arsenic acid--was 61%. For the insoluble compounds--arsenic trioxide and lead arsenate--the average mortality rate was a much lower 10%. A study in rats showed that the lethal dose of soluble sodium arsenite is only one-tenth of the lethal dose for the relatively insoluble arsenic trioxide. Thus, it appears that the water solubility of inorganic arsenicals influences their toxicity, possibly because the more soluble compounds are more available for absorption in the intestines.

Another factor that is considered important in determining the toxicity of inorganic arsenicals is the valence of the arsenic. It is generally accepted that trivalent arsenic is more toxic than pentavalent arsenic.[36,62] The difference in potency is demonstrated in animal studies such as those by Byron et al.[63] In their 2-y studies, six dogs were given 125 ppm of sodium arsenite in their diet and none survived; however, in a group of six dogs that were fed the same level of sodium arsenate, only one died. The researchers also fed sodium arsenite to rats and found no effects on growth and survival at dietary levels up to 62.5 ppm. In comparison, no effects were found in rats that were fed up to 125 ppm of sodium arsenate.[63] The arsenic also caused enlargement of the common bile duct in the rats at high doses, and the effects of arsenite were more severe than those of arsenate. For example, at 250 ppm, the number of enlarged common bile ducts was 45 of 49 in the arsenite-fed group and 25 of 50 in the arsenate-fed group.[63] In another study using mice, 10 mg/kg of sodium arsenite injected intraperitoneally caused embryotoxicity, but 25 mg/kg of sodium arsenate produced no embryotoxicity.[64] Demonstration of a difference in potency between arsenate and arsenite has not been made for humans. Neither has it been possible to differentiate human health effects caused by arsenite from those caused by arsenate.

MECHANISM OF ACTION

At the biochemical level, inorganic arsenic interferes with cellular respiration; the cells' ability to oxidize organic substrates and to produce the energy necessary for normal cell functions is inhibited. Arsenite and arsenate, however, appear to interfere with different steps in respiration. Arsenite has an affinity for binding to sulfhydryl groups, which results in the inhibition of enzymes and cofactors.[65,66] One important example of this is the binding of arsenite to dihydrolipoic acid, a required cofactor for some steps in the tricarboxylic acid cycle.[67,68]

Arsenate is believed to interfere with respiration by uncoupling oxidative phosphorylation. This interference may result from competitive substitution of pentavalent arsenic for pentavalent phosphorus and the formation of an unstable ATP (adenosinetriphosphate) analog that quickly hydrolyzes.[36] Arsenate is reported to have no affinity for thiols and, unlike arsenite, does not inhibit enzymes by binding to sulfhydryl groups.[69] As discussed previously, some researchers have found evidence that arsenate could be reduced to arsenite in vivo. The arsenite could then react with cellular enzymes and produce respiratory inhibition. Evidence also indicates that arsenite can uncouple oxidative phosphorylation; but unlike the proposed mechanism of arsenate, arsenite does it by stimulating mitochondrial ATPase activity.[70] The higher ATPase activity promotes the hydrolysis of ATP, thus reducing net ATP available for cellular functions.

The current understanding of the action mechanisms of arsenite and arsenate indicates that the two forms of arsenic act in generally different ways, but also suggests that overlapping or similar mechanisms exist as well. The two ways of uncoupling oxidative phosphorylation is an example. The overlaps may help explain why clearly different effects and potencies for arsenate and arsenite have not been found in human studies.

ACUTE AND SUBACUTE EFFECTS OF INORGANIC ARSENIC

Reports of human exposure to inorganic arsenic via ingestion include several in which the arsenic was consumed in drinking water. Where exposures were high enough to cause observable effects, the reports show that inorganic arsenic can affect several different organ systems. The most commonly affected systems include the circulatory, gastrointestinal, integumentary, nervous, hepatic, renal, and immune systems.

Table 2 summarizes the doses and effects reported in several different cases that are pertinent to establishing a 7-d drinking-water standard. In addition to subacute exposures, the table includes a few acute and chronic exposure reports that help to bracket a permissible 7-d exposure. The doses listed are, in most cases, rough estimates of total inorganic arsenic, made after the exposure took place. Similarly, the ratio of trivalent to pentavalent arsenic comprising the total inorganic arsenic is, in most cases, a rough estimate made after the period of exposure. The effects reported are those from cases severe enough to come to the attention of the public health authorities. Particularly in the cases of water or food contamination, the total number of people exposed is not generally known.

As shown in the second column of Table 2, the highest arsenic level reported in water that is not associated with any adverse health effects is 1 mg/L. The source of these data states that people were exposed to drinking water containing 0.05 to 1.0 mg/L.[71] Unfortunately, the report does not indicate how long people were exposed to water at the high end of this range. The report also states that the water with high arsenic content was used "without noticeable effect."[71] Presumably, this means that no effects were serious or prevalent enough to come to the attention of public health authorities and does not mean that a survey of the exposed population found no adverse effects.

This report also suggests that people may be able to tolerate levels of arsenic up to 1 mg/L for short periods of time without serious effects.[71] By contrast, other reports, listed in Table 3, show that such high levels cannot be tolerated for prolonged periods without producing serious, performance-degrading effects. Table 3 also shows that serious effects can develop if people are exposed to arsenic levels in excess of 0.4 mg/L (400 μg/L) for several years.[27]

The third incident listed in Table 2 is a report of severe arsenic poisoning caused by contaminated beer. In this case, the level of exposure in the affected individuals, as described by Reynolds, was determined by analysis of (1) the arsenic levels (2 to 4 mg/L) measured in beer after he began to see the occurrence of poisoning and (2) the amount of beer the affected individuals estimated they consumed (2 to 16 pints/d).[72] Thus, some of the affected individuals may have consumed as little as 2 mg/d of arsenic; however, because of the difficulties in trying to reconstruct exposure estimates after the exposure had occurred, the daily dose listed in Table 2 must be considered a rough estimate.

At an estimated exposure of about 3 mg/d (Table 2, incident 4), 417 people developed serious arsenic poisoning after, in most cases, 2 d of exposure from an accidental contamination of soy sauce in Japan.[74] The total number of people exposed was not

Table 2. Basis for 7-d drinking-water standard for inorganic arsenic.

Daily dose of total inorganic arsenic (mg)	Source of dose	Reported health effect	Exposure conditions	Reference
0.324 (high-dose group)	Drinking water	No clinical or hematological abnormalities	Long-term exposure[a]	24
0.1 to 2.0	Drinking water with 0.05 to 1.0 mg/L	No "noticeable effect"	Several months' exposure	71
~2 to 32	Contaminated beer with 2 to 4 mg/L	Digestive, circulatory, nervous, and integumentary systems affected; some deaths	Estimated consumption was ~1-8 L/d for several months	72,73
~3	Contaminated soy sauce	Digestive, circulatory, nervous, and integumentary systems affected; no deaths	2- to 3-wk exposure period	74
3.8	Arsenical medicine	Skin symptoms (cited as example of sensitive individual)	2-d exposure	75
20	Various	Acute intoxication	Single dose	76
70-180	Various	Fatal	Single dose	77

[a] The exposure period is described as "long-term," but the authors of the paper noted that it may have been shorter than the exposure period in other studies in which chronic arsenic intoxication was found (e.g., studies in Chile[78] and Taiwan[79]). Eighty-five percent of the residents in the study area had lived there for less than 10 y.[24]

Table 3. Basis for 1-y drinking-water standard for inorganic arsenic.

Arsenic level in drinking water	Effects found	Exposure period	Reference
3.8 to 16.5 μg/L average (5% of samples >100 μg/L)	No increase in incidence of skin cancer	Not determined	80
41 μg/L median (range, 1 to 4800 μg/L; mean = 347)	No dose response for arsenic ingestion; no signs of peripheral neuropathy	≥2 y[a]	81
50 μg/L (range, to 1400 μg/L)	Increase in arsenic accumulation in hair; no specific illness	Not stated	79
50 to 100 μg/L	Abnormal clinical findings in 16% of population, 10% in controls; abnormal EMG[b] in 17%, 0% controls	≥2 y[b]	82
>100 μg/L (range, to 1400 μg/L)	Abnormal clinical findings in 40% of population; abnormal EMG[b] in 50%	≥2 y[b]	82
180 μg/L and 210 μg/L average[c] (range, 53 to 750 μg/L)	No typical signs or symptoms	≥5 y	83
224 μg/L average (range, 1 to 2450 μg/L)	No effects	Long term[d]	24
410 μg/L (range, 160–590 μg/L)	Skin symptoms 21.6%, 2.2% in controls; higher prevalence of gastrointestinal symptoms in exposed population	≥8 y[e]	27
400 to 600 μg/L (range, 10 to 1820 μg/L)	Prevalence rates for hyperpigmentation, keratosis, skin cancer, and gangrene of extremities were 183.5, 71.0, 10.6, and 8.9/1000, respectively; contaminated well water	~50 y	39,78
598 μg/L average (range, 50 to 960)[f]	Skin changes, respiratory symptoms, cardiovascular effects, gastrointestinal symptoms	15 y	40

Table 3. (Continued)

Arsenic level in drinking water	Effects found	Exposure period	Reference
800 µg/L average	Skin changes, respiratory symptoms, cardiovascular effects, gastrointestinal symptoms	12 y	78

[a] Two out of the 147 participants were kept in the study because they had a high arsenic level in their drinking water (2655 µg/L) even though they had lived in the study area for only 13 months.

[b] The minimum time a patient with electromyographic (EMG) abnormalities had used a well with high arsenic concentration was 2 y. Exposure period for other study subjects not reported.

[c] Two "exposed" communities were studied, one with a mean arsenic concentration of 180 µg/L and one with a mean of 210 µg/L.

[d] The exposure period is described as "long-term," but the authors of the paper noted that it may have been shorter than the exposure period in other studies in which chronic arsenic intoxication was found (e.g., studies in Chile[78] and Taiwan[79]). Eighty-five percent of the residents in the study area had lived there for less than 10 y.[24]

[e] The shortest period of exposure after which lesions were detected was 8 y for hypopigmentation. Other skin symptoms had longer minimum exposure periods. No exposure periods were reported for the appearance of nonspecific symptoms (e.g., gastrointestinal symptoms).

[f] Average represents weighted mean from 1955 to 1970; range applies to same period.

reported. The fact that no one died as a result of the incident was attributed to early recognition of the problem and preventive measures.[74] The average duration of exposure to the 3 mg/d was estimated to be 2 to 3 wk. The primary symptoms included facial edema (>80%) and gastrointestinal symptoms such as anorexia (>80%), nausea (50%), epigastric fullness (50%), vomiting (35%), and abdominal pain (40%). Skin lesions, upper respiratory symptoms (e.g., headache, chill, sore throat, rhinorrhea), and signs of neuropathy also developed in about 20% of the affected cases.[74] These effects would certainly interfere with a soldier's ability to perform any kind of task.

Because the actual number of people exposed is not available, it is not known what percent of the population would be affected to the extent described. However, Holland's comment, that a patient reacting to a daily dose of 3.8 mg of arsenic in the form of As_2O_3

was an example of a sensitive individual, suggests that it would not be a large percentage.[75] A single oral dose of 20 mg is reported to produce severe acute intoxication,[76] and 70 to 180 mg can result in human fatalities.[77]

CHRONIC EFFECTS OF INORGANIC ARSENIC

Many studies document the effects of chronic exposure to arsenic in humans; in several of these, the arsenic was ingested as a drinking-water contaminant. The reported symptoms vary somewhat in different studies but characteristically include skin effects (pigmentation changes, keratosis, skin cancer), gastrointestinal disturbances, peripheral vascular disease, and neurological changes. The cancer and some of the nervous disorders may develop long after the period of exposure has ended.[52] The International Agency for Research on Cancer (IARC) evaluated the evidence for the carcinogenicity of inorganic arsenic and found "sufficient evidence that inorganic arsenic compounds are skin and lung carcinogens in humans," but that the data suggesting that arsenic causes cancer at other sites in the body are inadequate for evaluation.[84] Among the cases of cancer attributed to inorganic arsenic was that of a man who developed multiple skin carcinomas 11 y after an acute intoxication by arsenic in drinking water.[85] In another case, a woman ingested larger than normal (~14 cups of coffee per day) amounts of well water with 1.2 mg/L of arsenic; after 4 months, she developed skin, gastrointestinal, and peripheral nervous symptoms characteristic of arsenic intoxication. Twelve years later she began to develop multiple skin carcinomas of the type associated with arsenic (basal-cell carcinomas and squamous-cell carcinomas).[86]

Table 3 summarizes several epidemiology studies performed on populations exposed to inorganic arsenic in their drinking water for long periods of time. With a few exceptions, individuals in these studies were exposed to drinking water containing arsenic for at least 2 y (more typically, the exposures were much longer than 2 y). The first two studies in Table 3 found no increase in the incidence of skin cancer[30] or peripheral neuropathy[81] at mean total arsenic levels under 50 μg/L. At an average concentration above 50 (±30) μg/L, Goldsmith et al. found evidence of increased body storage of arsenic, as measured by increased levels of arsenic in hair, but no evidence of any specific illness associated with the arsenic.[87] The people in this study were consuming water with arsenic levels ranging from less than 0.1 mg/L to 1.4 mg/L.[87]

Hindmarsh et al. examined 92 people in Nova Scotia who were using well water with more than 50 μg/L of arsenic.[82] As noted in Table 3, the group with wells containing between 50 and 100 μg/L had a higher prevalence of clinical symptoms and of abnormal

electromyograph (EMG) readings than did the control group. The specific clinical symptoms found in the exposed groups were not given, and the reproducibility of some of the EMG readings has been questioned.[81] The group exposed to drinking water with arsenic levels above 100 μg/L (100 to 1400 μg/L) had an even higher prevalence of clinical symptoms and abnormal EMG readings. The clinical findings and EMG readings for the 50- to 100-μg/L group were all considered to be very mild effects, not severe enough to interfere with a person's ability to perform a complicated task such as driving a car.[88] The shortest exposure period for a person with abnormal EMG readings was 2 y.[82] Thus, it appears that a year of exposure to less than 100 μg/L would not produce a performance-degrading neuropathy. However, the delayed appearance of nervous system problems, as documented in other cases, cannot be ruled out.[52]

In another study, signs of arsenic intoxication were sought in two "exposed" groups of Utah residents: one with a mean total arsenic concentration of 180 μg/L in its water supply and another with a mean concentration of 210 μg/L.[83] The control group had a mean total arsenic level of 24 μg/L. All 145 members of the exposed groups and all 105 members of the control group had been residents of the community for at least 5 y. No evidence was found of arsenic intoxication in the form of statistically significant increases in the prevalence of anemia, dermatological symptoms, or neurological symptoms in the exposed groups. Southwick et al. did note among the exposed group, however, a slightly increased proportion of people with a slowing of nerve conduction.[83]

A similar study in an Alaskan community that had been exposed to a slightly higher level of arsenic (224 μg/L) also found no evidence of arsenic intoxication.[24] The health effects researched in this study were anemia, dermatological symptoms, and neurological symptoms. This study indicated that arsenic content in well water was not a reliable indicator of daily arsenic dose; many residents drank bottled water or drank a substantial proportion of their daily water at locations away from home (e.g., at work).

The last four epidemiology studies in Table 3 documented effects occurring when levels of arsenic in water exceeded 400 μg/L. In all of these studies, adverse effects typical of chronic arsenic intoxication were found; and in all four of these studies, the communities had been exposed to arsenic in their drinking water for several years. In Chile, Zaldivar documented the appearance of arsenic intoxication in babies after as few as 2 y of exposure.[40]

DEVELOPMENT OF RECOMMENDATIONS FOR STANDARDS

Major uncertainties exist in the method for calculating the recommended standards (7 d and 1 y) for arsenic, and in the data on which the calculations are based. In addition, assumptions were required to bridge gaps in the current knowledge about the health effects of arsenic.

METHOD AND RATIONALE

As previously described, arsenic accumulates in the body over time. For this reason, a standard for the maximum allowable 1-y exposure to arsenic should be lower than the maximum allowable 1-wk exposure. The recommended standard was derived by determining the maximum daily arsenic concentration that would produce no performance-degrading effects in troops after either a 7-d or a 1-y exposure. The maximum recommended daily doses are then diluted into an amount of water equivalent to the assumed water-consumption rates of 15 L/d and 5 L/d.

CALCULATION OF RECOMMENDATIONS FOR STANDARDS

The calculation for a 7-d and 1-y standard, using amounts of water equivalent to the assumed water consumptions of 15 L/d and 5 L/d are shown below.

Seven-day standard:

$$\frac{1500\ \mu g/d}{15\ L/d} = 100\ \mu g/L\ ; \qquad \frac{1500\ \mu g/d}{5\ L/d} = 300\ \mu g/L\ .$$

One-year standard:

$$\frac{320\ \mu g/d}{15/Ld} \approx 21\ \mu g/L\ ; \qquad \frac{320\ \mu g/d}{5\ L/d} = 64\ \mu g/L\ .$$

MAJOR UNCERTAINTIES AND ASSUMPTIONS

The choice of the daily arsenic doses that would not be expected to result in performance degradation required some assumptions about the proportion of different arsenic species present, the absence of other factors contributing to the observed effects, and the significance of arsenic from sources other than drinking water.

No-Performance-Degradation Dose (7 d)

Goudey reported (Table 2) that arsenic levels in Los Angeles aqueduct water reached levels as high as 1 mg/L, that "many people" were exposed to elevated arsenic levels for "several months," and that the exposed population was "without noticeable effect."[71] This incident involves the highest documented subchronic exposure level for humans where no reports were made of adverse health effects. In accepting this level as the basis for the 7-d drinking-water standard, we made the assumption that the 1-mg/L exposure (which was vaguely described) in the Owens Valley in Southern California occurred for a period of at least 1 wk (7 d). In addition, from the report of no noticeable effects, we inferred that no effects were found that would cause performance degradation in soldiers. If we assume that the average consumption of water during the period reported in Goudey's study (summer months of 1941) was 1.5 L/d, then the average dose at 1 mg/L would have been about 1.5 mg/d. (A literature survey by the National Academy of Sciences led to a calculated average, per capita, water-consumption rate of 1.63 L/d).[89] This is the source of the 1500-μg/d maximum dose used in calculating the recommended 7-d standard.

Another report, in which individuals were consuming similar amounts of inorganic arsenic, comes from the survey by Goldsmith et al. of individuals consuming water with high arsenic levels in Lassen County, California.[87] A health questionnaire revealed no evidence of any specific illness associated with arsenic among a population that included two individuals who drank water with about 1.4 mg/L of arsenic and one individual that drank water with about 0.8 mg/L of arsenic. The report did not state how long the individuals had been drinking the high-arsenic water, but presumably the exposure period was longer than 7 d. Because this is not a strong base from which to recommend a standard, the application of a safety factor should be considered.

No-Performance-Degradation Dose (1 y)

The mean arsenic concentration in the well water collected from the 59 Alaskan homes included in the study by Harrington et al. was 224 μg/L.[24] As mentioned previously, however, their study found that the arsenic level in well water was not a good indicator of an individual's daily arsenic dose. Instead, the various water sources used by study participants and the amount of water consumed from each source were determined before estimates of daily arsenic consumption were computed. The subjects were then divided into four groups based on their individual daily arsenic consumption. The group with the highest per person exposure ($\geq$ 100 μg/d) ingested an estimated daily dose of just

over 320 μg/per person of arsenic. The arsenic exposure of this group of 49 individuals appears to be the highest exposure level that did not produce adverse health effects, and it is the source of the 320-μg/d maximum dose used in calculating the recommended 1-y standard. The findings by Hindmarsh et al.[82] of a somewhat elevated prevalence of mild nervous system symptoms in a group exposed to arsenic levels of 50 to 100 μg/L are not used as the basis for the recommended standard because the reported symptoms are not judged to be performance-degrading.

Assumption of Similar Arsenic Species

Because we proposed a standard based on a no-effects level found in one study, we made an assumption that the ratio of trivalent to pentavalent arsenic in that study would be the same ratio found in water consumed by troops. This assumption may not be valid in all situations, as is demonstrated by the different trivalent-to-pentavalent ratios measured in some of the studies (Table 3). Southwick et al.[83] reported that pentavalent arsenic comprised about 86% of the total inorganic arsenic in one of the exposed Utah communities that was studied. A later report said that the low (20.0 μg/L) arsenic level in the control community was an equal mix of trivalent and pentavalent arsenic.[25] Five of the 59 samples of well water in the Alaska study were analyzed for arsenic species, and the percentage of trivalent arsenic in these samples ranged from 3 to 39% of the total.[24]

Assumption of No Additional Arsenic Sources

The standards recommended here assume that troops are exposed to no significant amounts of arsenic in either their food or the air. If substantial levels of arsenic do exist in either, then the maximum allowable levels of arsenic ingested with drinking water should be reduced.

RECOMMENDATIONS FOR STANDARDS

Various arsenic levels, either adopted or recommended as standards for drinking water, are shown in Table 4. The existing short-term (≤ 7-d) military standard of 2.0 mg/L appears to be dangerously high. The consumption of 2 L of water with 2.0 mg of arsenic per liter would deliver a dose one-third higher than that which caused arsenic poisoning in several hundred people in Japan within two days (Table 2, incident 4). The consumption of 15 L of water with 2.0 mg of arsenic per liter would deliver a dose 50%

Table 4. Comparison of drinking-water standards for arsenic.

Recommended standard (mg/L)		Assumed water consumption (L/d)	Source
≤ 7 d	≤ 1 y		
0.100	0.02	15	Maximum concentration recommended by this study
0.300	0.06	5	Maximum concentration recommended by this study
2.0	0.05	--[a]	TB MED-229[90]
2.0[b]	0.05[b]	5	QSTAG-246[91]
--	0.05	2	U.S. EPA[92]
--	0.05	2.5	WHO[93,94]

[a] Assumed water-consumption rate for purposes of calculating a recommended standard not stated.

[b] Minimum treatment requirements for assuring potability.

higher than that reported to produce severe acute intoxication (Table 2). The maximum allowable levels of 0.05 mg/L, proposed by the World Health Organization (WHO) and the U.S. Environmental Protection Agency (EPA) (Table 4), are apparently intended to protect against cancer. The 1-y standard recommended by this study is based on the highest exposure level that produced no adverse effect (including cancer) in a human population. The one-year standard recommended in this document for a 5 L/d consumption rate is approximately the same as the QSTAG (Quadripartite Standardization Agreement between America, Britain, Canada, and Australia) minimum treatment requirement for long-term consumption (>7 d and assumed applicable to a period of up to 1 y) at a rate of 5 L/d.

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CHAPTER 8. CYANIDE

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ABSTRACT

The objective of this chapter is to develop criteria and recommend military standards for cyanide in drinking water. These standards are intended to prevent performance degradation or irreversible effects in troops exposed for periods of up to either 7 d or 1 y to water that contains cyanide. The recommended standards are calculated with a one-compartment pharmacokinetic model and are based on the assumption that 0.5 mg/L is the maximum tolerable concentration of cyanide in whole blood. For an assumed water-consumption rate of 15 L/d, the recommended standard is 2 mg/L; for a 5-L/d consumption rate, the recommended standard is 6 mg/L.

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INTRODUCTION

We recommend the maximum concentration of cyanide in drinking water that can be tolerated without causing performance degradation or irreversible effects in military personnel. One standard is based on an assumed water-consumption rate of 15 L/d, and the other is based on 5 L/d. Water-consumption studies of men performing physical labor in hot climates, and U.S. Army field experience in desert situations, indicate that 15 L is a reasonable amount of water for troops to drink in one day. Five liters is a more reasonable expectation under less severe conditions.

We begin our assessment with a description of the chemical properties of cyanide that affect its toxicity and the likelihood of its presence at toxic levels in drinking water. We then briefly describe the most common and field-practical methods for measuring cyanide levels in water. Following this is a description of the pharmacokinetic (i.e., absorption, distribution, metabolism, and excretion) processes for cyanide in the body. An understanding of these processes is important because the recommended standards are based on calculations using a pharmacokinetic model. We also present a brief summary of the effects that cyanide produces in people, following acute and chronic exposure.

The last sections of this chapter describe how the recommended standards are calculated, and we make explicit the important assumptions incorporated in the recommendations. By making the methods and assumptions explicit, field decisions to modify the recommendations should be facilitated in situations where our assumptions do not apply. In addition, new findings regarding cyanide toxicity can be evaluated easily for their significance with regard to these recommended standards, and future updates should therefore be relatively easy to perform.

The recommended standards are designed to prevent cyanide toxicity. There appears to be no reason to expect that well-nourished military populations would suffer chronic cyanide toxicity if protected from the effects of acute exposures to cyanide in drinking water. Accordingly, the same standards are recommended for both short-term ($\leq$ 7 d) and long-term ($\leq$ 1 y) exposure periods. For the 15-L/d water-consumption rate, the recommended standard is 2 mg/L; for the 5-L/d rate, it is 6 mg/L.

GENERAL PROPERTIES

Among the various chemicals that contain the cyanide moiety (CN^-) and that can be found in water, hydrogen cyanide (HCN) is the form that is of the most toxicological importance. The cyanide anion (CN^-) can combine with elements of the alkali,

alkaline-earth, and heavy-metal groups to form many different compounds. In fact, it is cyanide's affinity for iron (Fe^{+3}) in the electron-transport chain that is responsible for its toxic effects. The cyanide moiety is also found in several different organic compounds that are commonly found in potential sources of drinking water. The toxic significance of the several types of cyanide-containing compounds depends primarily on the rate and extent to which they release CN^-. Primarily because it dissipates from water relatively quickly, HCN is found at health-threatening levels in water only under a limited set of circumstances.

According to Jenks,[1] the simplest inorganic cyanides are the cyanide salts, including the commonly used industrial salts, NaCN, KCN, and $Ca(CN)_2$. These salts are very soluble in water and are hydrolyzed to release free CN^- ions.[2,3] Other simple cyanide salts have varying solubilities in water.[3] Cyanide complexes can (metallocyanide ions or neutral species) also form with some metals, including iron, nickel, cobalt, zinc, silver, cadmium, and mercury. In water, these complexes dissociate to different degrees and release intermediate metallocyanide complexes, which can dissociate further into the metals and cyanide ions.[4,5] An example is the ferrocyanide complex, which is relatively nontoxic and which slowly releases CN^- into an aqueous solution. However, in the presence of ultraviolet light, the rate of cyanide release and the toxicity of the complex increase substantially.[6]

Cyanide can contaminate drinking water in several ways. The most important of these appears to be the discharge of cyanide-containing wastewater from industrial processes, particularly those associated with the metals industry. Industrial discharges have been implicated in most of the cyanide-pollution events serious enough to cause fish kills or to threaten human health.[7-10] Cyanide is used in the metal-processing industry for electroplating, heat treating (case hardening), and metal polishing.[1,11] Coal carbonization for the production of coal gas or in coke ovens generates large amounts of cyanide; in the past, this cyanide has found its way into water supplies.[8,12] Wastewaters from many mining operations contain cyanides that are used in the extraction of metals, such as gold and silver, from ore.[1,12]

Photograph and blueprint development frequently uses solutions of iron-cyanide complexes.[11] Another industry with a potential to release cyanides into the environment is chemical manufacturing, because cyanides are used in the production of dyes and pigments, agricultural chemicals, plastics, pharmaceuticals, and several other products.[1] Cyanides and their derivatives are also used in agriculture as pest fumigants, herbicides (cyanuric chloride), and fertilizers (calcium cyanamide).[1,4]

Microbial metabolism of nitrogenous compounds by bacteria, fungi, and algae can also be responsible for the presence of cyanide in water.[5,13] Microbial decomposition of

cyanide-containing plant material and domestic sewage constitutes a constant source of cyanide for some bodies of water.[9] Levels attributed to these sources, however, are much lower than those resulting from industrial or agricultural contamination.

The data in Table 1 show that most of the highest cyanide levels reported from water-monitoring studies are attributed to activities of the metals industry, particularly electroplating. Levels under 1 mg/L could cause fish kills,[18] but would not produce cyanide intoxication in humans. Undiluted and untreated industrial wastes from electroplating operations can contain cyanide levels from 0.5 to 20 wt%.[12] The last item in Table 1 shows that cyanide levels in the immediate vicinity of an industrial source can be high.[10] The fact that the monitoring studies shown in Table 1 did not find high cyanide levels in rivers and streams can be attributed to cyanide disappearing from water relatively fast. This disappearance can be explained partially by the tendency of HCN to volatilize. Under most natural conditions, the cyanide ion (CN^-) exists in water predominantly as HCN because HCN is a weak acid (pKa = 9.21). It is completely miscible with water.[2,19] At pH 7, less than 1% of the cyanide anion exists as free CN^-; but at pH 9, free CN^- and HCN would be present in about equal amounts. The boiling point of HCN is 26°C.[2] Reduction of cyanide levels in water can be aided by the presence of certain microorganisms that are capable of assimilating or mineralizing HCN.[13]

Chlorination of water that contains HCN results in the formation of the highly toxic cyanogen chloride (CNCl),[4] as well as the much less toxic cyanates (OCN^-).[11] Cyanogen chloride has limited solubility in water, can persist for more than 24 h, and slowly hydrolyzes to the cyanate ion.[8] Cyanates are able to persist in aerobic water at pH 7 and 20°C for 10 d.[20] Under properly controlled conditions, chlorination can be used to convert cyanides in the water to nitrogen, carbon dioxide, and small amounts of nitrate.[8] Under acidic conditions, cyanate is converted to ammonia,[21] which can cause toxicity or odor problems if present at sufficiently high levels.

DETECTION OF CYANIDE

Several different techniques are available that are capable of measuring levels of cyanides in water at or below levels of concern to human health. Detection methods include colorimetric and titrimetric procedures, as well as the use of a cyanide-ion selective electrode.[21] Because most cyanides are reactive and because there are several substances commonly present in water that will interfere with the measurement of cyanides, sample-preservation and sample-preparation (e.g., distillation) steps are generally recommended.[21]

Table 1. Cyanide levels in several waters.

CN^- concentration (mg/L)	Description of water	Reference
0.0001 to 0.008[a]	Brook, Northern Eifel National Park, Germany	9
<0.008[b]	Survey of 969 public water supplies in U.S.	14
0.03 to 0.06 (maxima)	11 Canadian streams	15
0.10[c]	Tap water from 43 towns in England	16
0.06 to 0.20 (maxima) 0.02 to 0.05 (means)	Two contaminated rivers, Barcelona, Spain	10
≤ 0.20	River water contaminated by metals industry, Germany	9
≥ 0.20	Estuary with coke-oven contamination, England	17
0.07 to 0.56 (maxima) 0.04 to 0.41 (means)	Industrially contaminated water conduits, Barcelona, Spain	10
25.6 to 37.0 (maxima) 20.1 to 26.8 (means)	Samples taken from gutters in zone with metals industry, Barcelona, Spain	10

[a] Total cyanide measured.

[b] Report notes that concentrations in samples may have decreased during transportation to laboratory.

[c] Maximum concentration found; 42 of 43 samples were <0.05 mg/L.

Cyanide levels in water are reported generally as "total cyanide"; but as previously mentioned, not all forms of cyanide found in water are equally toxic. Some of the cyanometal complexes, the cyanates, and thiocyanate are substantially less toxic than cyanogen chloride or HCN. Thus, the toxicological significance of "total cyanides" depends on the proportion of the more toxic vis-a-vis the less toxic forms of cyanide present. Methods for differentiating various forms of cyanide are available.[21]

The detection of cyanide is not part of the standard water-quality-analysis tests performed by military personnel in the field. Generally, the test is performed if the presence of toxic chemical agents, such as cyanide, is suspected in raw water.[22] The test for cyanide is one of several in a portable, lightweight kit (the newly introduced M272 Water Testing Kit for Chemical Agents) that will detect chemical warfare agents in water.[22] Currently, the cyanide test is colorimetric and reliably detects cyanide as CN^- at a concentration of 20 mg/L within 1 to 5 min, depending on temperature (e.g., 1 to 2 min at ambient temperature, less than 1 min at 52°C, and 2 to 5 min at 0°C).[22,23] According to Eckhaus,[24] however, current research under a Product Improvement Plan (PIP) focuses on increasing the sensitivity of the test, enabling detection of CN^- at concentrations that are at least a factor of 4 below the current detection limit (i.e., $\leq$5 mg/L, compared to 20 mg/L).

Cyanide is commonly known to have the characteristic odor of burnt almonds; however, anecdotal reports of individuals unable to detect their own exposure to dangerous levels of cyanide suggest that odor cannot be relied on as a warning against cyanide poisoning.[25] Kirk and Stenhouse[26] found that 5 of 112 females and 24 of 132 males were unable to distinguish a 20% KCN solution from distilled water. Gwilt[27] states that a sensitive nose can detect cyanide in solution once the concentration exceeds 1 to 2%. Unfortunately, he does not refer to the basis for the statement. His estimate that 20 to 40% of the population cannot detect cyanide by odor is often quoted, and it is based primarily on anecdotal reports in which the concentration of cyanide being smelled was not measured.[27]

PHARMACOKINETICS

Gastrointestinal absorption is rapid and is influenced by various factors. Studies indicate that cyanide is distributed rapidly and widely within the body. As will be discussed, cyanide inhibits the body's use of oxygen by blocking the chain of reduction and oxidation reactions of cellular respiration. Thus, the accumulation of cyanide in the intracellular spaces, where electron transport occurs, is critical to the development of

cyanide toxicity. Many studies demonstrate the rapid conversion of the cyanide ion to the less toxic thiocyanate ion. Whereas fairly large quantities of cyanide can be metabolized within a day, the limiting factor in determining a tolerable cyanide exposure is the rate of dose administration. The threat of acute poisoning arises when cyanide dosing overwhelms the detoxification mechanism. Many studies on cyanide excretion indicate that the body normally eliminates cyanide almost exclusively in the urine, as thiocyanate. It is also possible that significant amounts of cyanide might be eliminated through perspiration during periods when large quantities of sweat are being lost.

ABSORPTION

Consistent with its reputation as a rapidly acting poison, ingested cyanide is believed generally to be absorbed rapidly from the gastrointestinal tract.[28-30] In the acidic environment of the stomach, the nonionic HCN form predominates and can be expected to diffuse through the lipophilic cell membranes of the intestinal mucosa. No quantitative data on the rate of gastrointestinal absorption of HCN were found. Dugard and Mawdsley[31] demonstrated the permeability of cell membranes to HCN when they measured the rate of cyanide diffusion across human skin (stratum corneum). They found that the maximum permeability constants for CN^- and HCN were proportional to the concentration, were strongly dependent on pH, and that the HCN permeability constant was 25 times higher than that of the CN^- ion. The rapid appearance of toxicity following the inhalation of HCN fumes also suggests that HCN is rapidly absorbed through the lungs.[29,30]

DISTRIBUTION

Once absorbed into the blood, cyanide is distributed to all organs of the body. Detoxification of cyanide, however, can occur in the blood prior to tissue distribution. When absorption is from the gastrointestinal tract, the liver is the first major organ through which the cyanide-containing blood must pass. As will be described, substantial detoxification of cyanide to thiocyanate occurs in the liver. By contrast, when cyanide is absorbed from the lungs, a larger fraction of the absorbed dose is distributed as the most toxic, unmetabolized form, HCN. The lack of detoxification after inhalation is an important consideration when dose-response data from an inhalation exposure are used to establish a standard for cyanide in drinking water.

The most important target for cyanide in the body is the mitochondrial-bound enzyme, cytochrome oxidase. Because mitochondria are intracellular structures, the

intracellular cyanide concentration is critical in cyanide poisoning. Unfortunately, the measurement of this concentration is not easy. Blood levels are used frequently as a convenient, but indirect, measure of cyanide body burdens. However, blood levels may not follow intracellular levels[32]; this must be considered when blood levels are the measure of dose used to predict cyanide poisoning.

Because exposure to cyanide from food and smoking is common, small amounts can be detected in the tissues of healthy people[32] (up to 50 μg/kg have been reported[33]). When larger doses are administered, the organs that first show signs of cyanide intoxication appear to be those that are the most sensitive to the anoxia caused by blocked cytochrome oxidase, notably the heart and brain.[34] Following large doses, the different amounts of cyanide measured in different organs appear to be related to the amount of blood in the organ.[32] Although cyanide binds to certain enzymes in the body, no evidence exists of cyanide-ion accumulation in the body after repeated administration.

METABOLISM

The enzymatic conversion of cyanide (CN^-) to thiocyanate (SCN^-) (Fig. 1) is the primary route by which cyanide is metabolically detoxified.[36,37] This route can account for as much as 60 to 90% of metabolized cyanide in mammals.[35] Rhodanese is the enzyme primarily responsible for this detoxification, but the enzyme mercaptopyruvate sulfur transferase can also transform CN^- to SCN^-.[38] Figure 1 also illustrates several other routes of cyanide metabolism. McNamara[39] estimated that the overall rate of metabolism of intravenously injected HCN in humans is about 0.017 mg/(kg • min).

In what may be the largest of the so-called minor metabolic routes, cyanide reacts with cystine to form iminothiazolidine. Following injection of 29 mg of KCN into a rat over an 8-d period, about 15% of the injected cyanide was metabolized by this route.[40] Temporary elevation of iminothiazolidine levels in the saliva of occupationally exposed individuals provides good evidence that this metabolite is also formed in humans.[40] This reaction is thought to proceed without enzymatic mediation.[40] The rapid elimination of unaltered iminothiazolidine after its injection into rats indicates that it can be considered as a detoxification product.[40]

Cyanide also binds to hydroxycobalamin to form cyanocobalamin (vitamin B_{12}).[41-43] Because vitamin B_{12} is of low toxicity, its formation also can be viewed as a detoxification product.[44,45] However, because the amount of hydroxycobalamin normally in the body is small, the formation of cyanocobalamin appears to be a route by which no more than 25 μg of cyanide would be detoxified.[43]

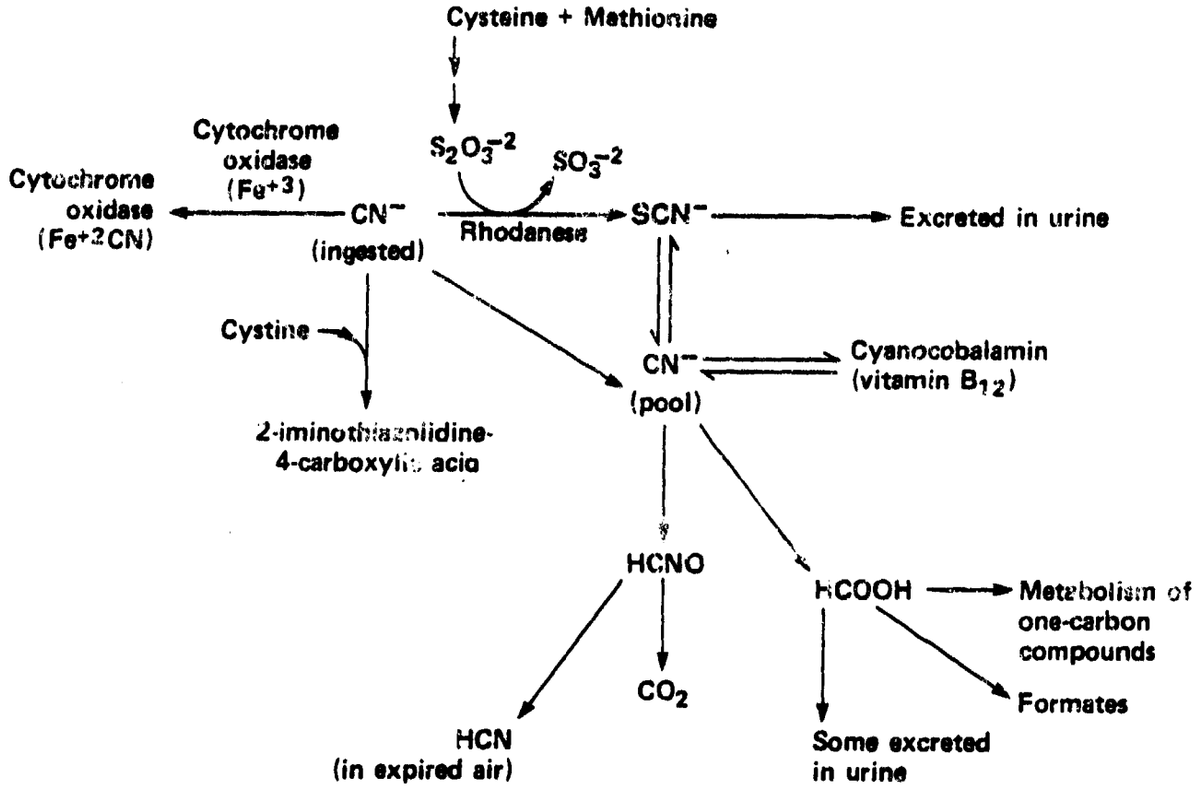

Figure 1. Schematic diagram of mammalian cyanide metabolism. Adapted from Williams.[35]

Chronic exposure to cyanide may adversely affect the health of some individuals by accelerating the elimination of vitamin B_{12}, thereby contributing to a deficiency of the vitamin. This effect has been shown in animal studies in which administration of cyanide to rats appeared to cause a depletion of vitamin B_{12} in the liver.[46,47] Wilson and Matthews[48] examined humans and found an inverse correlation between blood levels of cyanide and vitamin B_{12}.

Studies in dogs and rats with carbon-labeled cyanide showed that the cyanide carbon enters the metabolic pathway for one-carbon compounds.[41] Evidence for this was the appearance of labeled carbon in formate and CO_2, as well as in the methyl group of methionine and choline. The authors postulated that cyanide and thiocyanate might be converted to CO_2 via cyanate.

Rhodanese (thiosulfate sulfur transferase) catalyzes the addition of sulfur to a thiophilic anion (e.g., CN^-) to form a new thiolated anion (e.g., SCN^-). Rhodanese has been isolated, characterized, and tested by several researchers.[49-54] Thiocyanate (SCN^-) has a much lower acute toxicity than cyanide (CN^-),[55,56] but chronic exposures can produce adverse effects, including nervous system degeneration and goiter.[55,57] Because thiocyanate is considered to be much less toxic than cyanide, this reaction is also characterized as a detoxification process.[36,37]

Although rhodanese is present in several different organs in the body, most of it is found in the liver.[49,58,59] The level of rhodanese in the brain and muscles is much lower than in the liver; however, the relatively large mass of these organs and the high volume of blood flowing into them suggest that substantial amounts of cyanide could be detoxified in them as well.[49] Because rhodanese is found primarily in the mitochondria,[60,61] it is necessary that the source of sulfur for the detoxification process also be present within the cell.

Because the body has enough rhodanese to metabolize several fatal doses of cyanide within a 15-min period, depletion of endogenous sulfur is generally believed to be the limiting factor in cyanide detoxification.[37,49,62] Amino acids that contain sulfur appear to be the major, ultimate sources of sulfur for the formation of thiocyanate. Other sulfur-containing substances including thiosulfate, organic sulfanes, sulfate, and colloidal sulfur can also donate sulfur for the formation of thiocyanate (sulfane sulfur is a divalent sulfur covalently bonded only to another sulfur atom).[53] It is not known whether all of these can act as substrates in the final, rhodanese-catalyzed step of detoxification.

As demonstrated in both *in vitro* and *in vivo* studies, thiosulfate ($S_2O_3^{-2}$) can serve as a sulfur source for thiocyanate formation.[49,63-66] Sylvester *et al.*[66] found that administration of thiosulfate to dogs accelerated the conversion rate of cyanide to thiocyanate approximately 30-fold. Based on this information, some researchers are

convinced that thiosulfate is the endogenous source of sulfur in the natural, mammalian metabolic conversion of cyanide to thiocyanate.[62,67] Others, however, do not believe that the endogenous source of sulfur has yet been proven.[18,36]

Whatever form of sulfur is used in the rhodanese-catalyzed reaction, sulfur-containing amino acids appear to be the ultimate source of most of the sulfur for thiocyanate formation.[55] For example, Wood and Cooley[40] showed the production of labeled SCN^- from ^{35}S-cystine, even though cystine is not a substrate for rhodanese. Barrett et al.[68] showed that methionine can be a major contributor of sulfur in the rhodanese-mediated detoxification of cyanide, but that inorganic sulfate can also contribute a small amount of sulfur to the reaction. Saunders and Himwich[50] also showed that cystine could donate sulfur for the reaction.

Westley[53] described the interconversions between the several sulfane compounds in the body and explained how cyanide could deplete these compounds. Depletion of the compounds in the sulfane pool could interfere with the normal functioning of any process requiring one of these compounds.[53] Thus, cyanide could indirectly affect a large number of the body's biochemical functions.

If sulfur-containing amino acids are the ultimate source of sulfur for the formation of SCN^- (i.e., the detoxification of CN^-), then populations with protein-deficient diets could be particularly sensitive to the toxic effects of CN^-. This is speculated to be a contributing factor to some of the endemic adverse health conditions (e.g., neuropathies, goiter, and diabetes) reported to occur in cyanide-exposed populations of tropical Africa and the Caribbean. A study involving protein-deprived rats supports this hypothesis. Rosenthal et al.[69] found a 68% loss in the in vitro rhodanese activity of liver excised from rats after 2 wk of protein deprivation. This was associated with a 43% loss of liver protein.[69]

Some of the chemical properties of thiosulfate are consistent with the hypothesis that depletion of an endogenous source of sulfur enhances cyanide toxicity. For example, thiosulfate is a large divalent anion that would not be expected to penetrate the cell and mitochondrial membranes readily, thus coming in contact with mitochondrially bound rhodanese. Therefore, when given as an antidote, high plasma levels of thiosulfate must be maintained to encourage diffusion through the membranes.[49] There is also evidence that thiosulfate may cross the mitochondrial membrane with the aid of a protein carrier.[70] Thiosulfate appears to be produced naturally in small amounts, and its production does not increase in response to CN^- exposure.[62]

Metabolism of sulfur-containing amino acids is believed to be the source of endogenously produced thiosulfate.[71] The addition of thiosulfate to in vitro preparations of mitochondria causes them to swell. Presumably, the swelling is associated with an enhanced permeability of the mitochondrial membrane.[64]

Once thiocyanate is formed, most of it is excreted; however, some may be reconverted to cyanide.[41] This conversion was reported to be catalyzed by red blood cells and involved an enzyme named thiocyanate oxidase.[72] Thiocyanate can also react with hydrogen peroxide to release cyanide according to the reaction[55,73]:

$$SCN^- + 3\ H_2O_2 \rightarrow CN^- + SO_4^{-2} + 2\ H_3O^+ \ .$$

Chung and Wood[74] suggested that oxyhemoglobin may act as a peroxidase for the release of cyanide from thiocyanate as well. The extent to which thiocyanate releases cyanide before it is excreted is not known,[57] and whether the release occurs in vivo at all is controversial.

ELIMINATION

Most of the cyanide is eliminated rapidly from the body as thiocyanate in the urine. Other routes of elimination exist for cyanide and its metabolites, but they only account for a small fraction of the removal of the absorbed dose. For example, small amounts of cyanide have been measured in the breath, feces, sweat, and saliva of exposed humans and animals. However, it is conceivable that a significant amount of cyanide could be lost in sweat when sweat losses are excessive. There is no evidence that cyanide accumulates in the body, or that repeated cyanide exposures alter the metabolites recovered in urine or feces.

Elimination via Urine

In several studies, the elimination of cyanide was measured in the urine, breath, and feces of animals. Researchers found that urine is the primary route of elimination for absorbed cyanide. For example, Okoh injected 16.6 μmol of $Na^{14}CN$ into five previously unexposed rats.[75] The percentages of administered radioactivity recovered at the end of 24 h in three routes of elimination were 57% in the urine, 4.5% in expired air, and 1.1% in the feces. Thiocyanate (SCN^-) accounted for 79% of the radioactivity recovered in the urine, CN^- accounted for 1.3%, and CO_2 accounted for 6.1%.

Crawley and Goddard[76] found similar results when they injected rats with about 6 μg/kg of ^{14}C-labeled potassium cyanide. At the end of 24 h, 45% of the administered radioactivity had been recovered in the urine. At the end of 60 d, 74% was recovered in the urine, 8% in expired air, and 15% in the feces. Identification of the chemical species containing the ^{14}C was not performed. When Okoh and Pitt[77] looked for eliminated radioactivity 9 h after the dosing of rats with $Na^{14}CN$, they found 25% of the injected radioactivity in the urine, 4% in the breath, and 0.6% in the feces.

Tolbert and Hughes[78] also measured the radioactivity in the urine, breath, and feces of animals injected with $Na^{14}CN$. Using mice, they reported a slightly different elimination pattern than the similar studies cited previously. After 24 h, only 34% of the administered dose had been eliminated in the combined urine and feces sample, but 15% had been eliminated in the breath. At the end of 30 d, 72% had been eliminated in the urine and feces, and 25% in the expired air. Most studies performed subsequent to this investigation reported smaller amounts of ^{14}C eliminated in the expired air.

In a few additional studies, elimination of radiolabeled carbon was measured in urine and/or breath but not in feces. Most of the findings were consistent with those from the studies in which all three routes of elimination were monitored. For example, Boxer and Rickards[41] found that, within 9 d following subcutaneous injection into rats, 51% of the dose was recoverable in the urine as thiocyanate. Turner[79] administered a dose to opossums and recovered 46 to 57% in the urine within 2 d and 62 to 72% within 6 d. Christel et al.[80] administered a dose to dogs and recovered 35 to 60% in the urine within 6 d. About 75% of the amount recovered after 6 d was recovered within 1.5 d.[80]

In two studies, researchers examined the elimination of cyanide via the urine soon after the cyanide was administered. Burrows et al.[81] injected cyanide subcutaneously into mice and recovered from the urine about 7 to 9% of the administered dose within 3.5 h. In a similar study using dogs, Christel et al.[80] recovered 0.3% of the administered dose from the urine within 3 h; of the recovered cyanide, approximately 80% was recovered as cyanide. These studies suggest that some urinary elimination of cyanide from the body begins almost immediately after it is absorbed and before substantial conversion to thiocyanate occurs.

As previously mentioned, most of the cyanide dose recovered from urine was in the form of thiocyanate (SCN^-). Okoh and Pitt[77] collected and analyzed the urine samples of rats over a 9-h period after dosing with $Na^{14}CN$; they found 71% of the ^{14}C as SCN^-, 5% as CO_2, and 1% as CN^-. Similarly, in another study,[75] 71% of the cyanide in a sample collected for 12 h was in the form of SCN^-. A longer collection period in the same study resulted in a slightly higher (79%) recovery of the administered dose as SCN^-. Turner[79]

reported that more than 90% of the cyanide eliminated in the urine of opossums was in the form of thiocyanate. Within 8 d after dosing, Wood and Cooley[40] reported that 79.5% of the cyanide recovered from the urine of a single rat was in the form of SCN^-. In contrast, Boxer and Rickards[41] reported that 51.1% of the cyanide recovered from the urine of rats within 9 d was in the form of SCN^-. With an apparently anomalous result, they administered a dose to a single dog and recovered from the urine only 7% in the form of SCN^- after 7 d.

Other Metabolites in Urine

In addition to thiocyanate, the labeled carbon from cyanide has been recovered from urine as a part of several different metabolites, including 2-iminothiazolidine-4-carboxylic acid, cyanocobalamin, CO_2, formate, allantoin, and free cyanide (CN^-). It appears that the cyanide species, other than thiocyanate, normally amount to less than 20 to 30% of the total cyanide in the urine. Wood and Cooley[40] detected the presence of 2-iminothiazolidine-4-carboxylic acid in the urine of two rats that had received high doses of cyanide (about 100 mg/kg over 1 wk). The measured metabolite in one of these samples corresponded to about 15% of the administered dose. No comparative measurements were made on the urine of rats that had not received cyanide. Smith and Foulkes[82] were unable to detect any 2-iminothiazolidine-4-carboxylic acid in the urine of rats that had been given 1 mg of KCN per week for a period of 20 wk, and Turner[79] detected only a trace amount of the metabolite in the urine (collected for 2 d) of opossums that had received a single dose of 3 mg of NaCN per kilogram of animal body weight.

Because hydroxycobalamin is present in the human body in such small quantities, cyanocobalamin is believed to account for only a small fraction of the cyanide eliminated from the body.[43] However, not much data exist on cyanocobalamin levels in urine to support this. After injecting radiolabeled cyanide into a dog, Boxer and Rickards[41] found only about 0.01% of the injected radioactivity as cyanocobalamin in the urine. This amount was about two times more than that found as labeled free cyanide (CN^-). In a study designed to evaluate the effectiveness of hydroxycobalamin as a cyanide antidote, Mushett et al.[45] found cyanocobalamin in the urine at higher levels than SCN^- or CN^-. The mice in this study were injected with 100 mg/kg of hydroxycobalamin following their dosing with cyanide. As a result, 9.6% of the administered 550 μg of cyanide was recovered as cyanocobalamin, 3.5% as SCN^-, and 0.7% as CN^- within 2.5 h. Radiolabeled formate and allantoin of low specific activity were isolated from the urine of a dog that Boxer and Rickards[83] injected with $Na^{14}CN$.

Elimination via Expired Air

The data on elimination of cyanide shows that the body rids itself of much more cyanide in the urine than in expired air. However, some of the labeled carbon from administered cyanide (i.e., several percent) is recoverable from the expired air of animals; almost all of this is found as $^{14}CO_2$ rather than as $^{14}CN^-$.

In several studies, ^{14}C-labeled cyanide was administered to rats or mice. For example, Burrows et al.[81] recovered 4 to 5% in expired air within 3.5 h (mice); Tolbert and Hughes[78] recovered 10% within 6 h (mice); Okoh and Pitt[77] recovered 4% within 9 h (rat); and Okoh[75] recovered 4% within 12 h (rat). Boxer and Rickards[83] gave repeated doses of cyanide (i.e., 5 doses at 215 μg of $Na^{14}CN$ per dose) to rats for 5 h; at the end of 7 h, they recovered only 1.7% of the total administered dose. Other recoveries of cyanide reported for 24 collection periods were 3.6%,[76] 4.5%,[75] and a much higher 15%.[78] One week after injection, Crawley and Goddard[76] recovered 8.0%; at the end of 2 wk, they recovered 8.3%. Burrows et al.[81] have commented that the use of the metal counting chamber to measure levels of the highly reactive cyanide in the Tolbert and Hughes[78] study may account for the high levels they reported.

In a few of the studies where the labeled cyanide carbon was recovered, the chemical species of the ^{14}C was also determined. Okoh and Pitt[77] measured 86% as CO_2 and 14% as free cyanide in their sample that was collected over 9 h. Okoh[75] reported 86% as CO_2 and 13% as free cyanide (12-h collection period) and 91% CO_2 and 9% free CN^- (24-h collection period). Boxer and Rickards[83] reported that about 90% of the ^{14}C they recovered during their 7-h collection period was as CO_2 and 10% was free cyanide.

Elimination of the cyanide carbon in the expired air begins very soon after the cyanide dose is administered. Okoh[75] detected it within 10 min after injecting rats with cyanide, and Tolbert and Hughes[78] reported that the peak elimination rate was attained within 6 to 10 min after administration. The data discussed above also show that most of the elimination via expired air occurs within the first few to several hours after administration. Thus, it appears that less than about 10% of cyanide carbon is eliminated in expired air.

Elimination in Feces

Because thiocyanate is present in both the saliva[84] and gastric juice,[85] it is reasonable to expect thiocyanate to be present in the feces. In three studies, researchers have examined this pathway by looking for radioactivity in the feces following the injection of a radiolabeled (^{14}C) cyanide salt into rats. Okoh and Pitt[77] collected feces

samples for 9 h after administration of a dose and found that 0.09% had been eliminated in the feces. Okoh[75] found 1.3% in a 12-h sample of feces and 1.8% in a 24-h sample. Crawley and Goddard[76] collected feces samples for a longer period of time and reported finding 4.3% of the applied dose in the 24-h sample, 14.3% in the 7-d sample, and 15.1% at the end of 2 wk. After 2 wk, the ^{14}C levels in the feces were below detectability. None of these studies determined the chemical species containing the ^{14}C. However, Okoh and Pitt[77] did analyze the radioactivity in a sample consisting of the contents and tissue of the large intestine 9 h after administration of $Na^{14}CN$. They found that 58% of the total activity in that sample was SCN^-, 9% was free CN^-, and 1% was CO_2. Thus, it appears that elimination via feces is not significant during the first few days but may account for several percent of the metabolites cleared after 1 wk.

Elimination in Sweat

Perspiration is a potentially significant elimination pathway for cyanide, particularly in those situations in which large volumes of sweat are being lost. Maximum sweat losses from unacclimated individuals are 1.5 L/h, and maximally acclimated individuals can lose as much as 4 L/h.[86] Thiocyanate concentrations in human sweat have been measured at levels of 1.64 mg/L in an "unexposed" nonsmoker,[87] 6.96 mg/L in a smoker,[87] and about 6 mg/L in an individual given 1500 mg of NaSCN.[88] Assuming an imperceptible sweat loss of 1 L/d, Moister and Freis[88] estimated that the thiocyanate eliminated in the sweat of a human subject over a 13-d period amounted to about 4% of an administered dose of 4440 mg of KSCN. The dose was taken orally over a 13.3-d period.

The mean plasma concentration was not given for either the individual smoker or the nonsmoker whose thiocyanate concentrations were measured in sweat. However, the mean plasma concentration of the group of smokers was reported as 7.10 mg/L, and the mean of the nonsmokers' group was 1.96 mg/L.[87] A plasma concentration of 35 mg/L of thiocyanate (4.9 mg KSCN per 100 mL) was reported in an individual whose sweat contained 8 mg/L of KSCN.

Personnel under heat stress and losing sweat at 2 L/h would rid themselves of thiocyanate at about 12 to 14 mg/h if concentrations of thiocyanate in sweat similar to those mentioned previously (i.e., 6 to 7 mg/L) were maintained. This would correspond to the elimination of about 6 to 8 mg/h of cyanide ion. It thus appears that the normal elimination of thiocyanate may be substantially altered by large sweat losses.

No measurements of the levels of unmetabolized cyanide in sweat were found in the literature. If cyanide can also be excreted in the sweat, especially during periods of high sweat loss, this could represent an important mechanism for removing high concentrations of cyanide from the blood.

HEALTH EFFECTS

Cyanide is known to cause acute health effects by blocking electron transport, thus preventing the body from using oxygen. In addition, cyanide has been associated with a few chronic conditions in some susceptible populations. These chronic conditions may be related to long-term exposure to low levels of cyanide.

EFFECTS OF ACUTE EXPOSURE TO CYANIDE

The cyanide ion is detoxified rapidly to thiocyanate; therefore, the accumulation of an acutely toxic level of cyanide will occur when the rate of dosing exceeds the rate of detoxification plus excretion. The effects produced by a given amount of cyanide will be influenced strongly by the period of time over which the dose is administered. Once a toxic concentration is accumulated, the cyanide exerts its effects rapidly, acting as a chemical asphyxiant and preventing the use of oxygen in cellular respiration. The nervous and respiratory systems are the first to fail in severe cyanide poisoning.

Table 2 shows concentrations of cyanide that were measured in whole blood and the health effects observed at the reported concentration. The entries at the top of the table are examples of background levels measured in healthy people, illustrating that a measurable level of cyanide is normally present in human blood. The levels reported in Table 2 from the work by Symington et al.[91] are means; individual values ranged up to 0.32 mg/L for nonsmokers and 0.52 mg/L for smokers. These are much higher than the levels reported by Chandra et al.[89] and Ballantyne.[90] This may be due to the use of a different analytical method, or it may be due to the long interval between the time the blood samples were taken and the time the samples were analyzed. The storage conditions for the blood samples in the study by Symington et al.[91] can cause cyanide formation.[90,101] A group of workers exposed to cyanide gas and alkali-cyanide salts via inhalation, reported by Chandra et al.,[89] had mean cyanide blood levels of about 0.2 mg/L (see Table 2). The high mean (i.e., 0.56 mg/L in Table 2) for the smoker group is due primarily to one very high value (2.2 mg/L); if this one measurement is excluded, the mean becomes 0.23 mg/L.[89] Symptoms reported for the workers included headache,

Table 2. Blood-cyanide concentrations and health effects.

Cyanide concentration whole blood (mg/L)	Population	Health effect	Reference
	Background level:	None	89
<0.086	nonsmoker;		
<0.094	smoker		
	Background level:	None	90
0.016	nonsmoker;		
0.041	smoker		
	Background level:	None	91
0.08	nonsmoker;		
0.18	smoker		
0.18	Occupationally exposed nonsmoker	"Typical complaints"[a]	89, 92
0.56 (0.23)[b]	Occupationally exposed smoker	"Typical complaints"[a]	89, 92
0.2	Humans	Suggests toxic reaction	93
0.22	SNP-treated[c] humans	None	94
0.51	SNP-treated[c] humans	Apparent threshold for metabolic effects	95, 96
0.90	SNP-treated[c] humans	Metabolic acidosis	95
1.0 to 10	Human poisonings	Toxicity and lethality	97
1.82[d]	Mice	Lethal	98
2.00	Dogs	No effects	99

Table 2. (Continued)

Cyanide concentration whole blood (mg/L)	Population	Health effect	Reference
2.90 to 28.7	Humans	Lethal	100
7.00 to 10.0	Dogs	Lethal	99

[a] Headache, weakness, palpitation, nausea, breathlessness, and tremors.

[b] Mean concentration if the highest concentration measured for one of 8 subjects (2.2 mg/L) is not included.

[c] SNP = sodium nitroprusside.

[d] Blood concentration after a lethal dose (intraperitoneal administration) to 50% of a population of laboratory mice.

breathlessness, weakness, palpitation, nausea, giddiness, and tremors--typical symptoms of cyanide poisoning.[92] It is important to note, however, that these symptoms were probably due to elevated inhalation exposures and associated blood cyanide levels. Consequently, mean blood levels are not necessarily indicative of toxicity. Other symptoms noted for the workers, including pain/irritation in the throat and eyes, are attributable to the irritating properties of the alkali-cyanide-salt aerosols rather than to the cyanide itself.[102]

Berlin[93] and Rumack and Peterson[29] have offered the opinion that whole-blood concentrations above 0.2 mg/L may cause cyanide intoxication. Pasch et al.[94] recommended a whole-blood concentration of about 20 nmol/mL of erythrocytes (this corresponds to a whole-blood cyanide concentration of 0.22 mg/L, based on a ratio of 0.42 mL of red blood cells per mL of whole blood[103]) as a level that would present no danger to patients. Actual measurements of blood cyanide in patients that had received the cyanide-releasing drug, sodium nitroprusside (denoted as SNP; $Na_2Fe(CN)_5NO \cdot 2H_20$) show that detectable metabolic effects do not occur until about 1 mg/L (see Table 2). Aitken et al.,[95] for example, detected metabolic disturbances in patients administered SNP when whole-blood cyanide levels were above 0.9 mg/L. An apparent threshold was 0.53 mg/L of cyanide in blood. They recommended that short infusions of SNP be limited to 0.5 mg/kg, which is equivalent to 0.18 mg CN/kg, assuming that 4 of the 5 cyanide molecules in SNP are released.[98] Pasch et al.[94] indicated that cyanide concentrations

above 200 to 250 nmol/mL in red blood cells (i.e., 2.2 to 2.7 mg/L in whole blood) can produce severe clinical symptoms, and concentrations above the range 400 to 500 nmol/mL (i.e., 4.4 to 5.5 mg/L in whole blood) are lethal. Michenfelder and Tinker[99] indicated that whole-blood cyanide levels above 5 μg/mL (5 mg/L) are toxic. Cyanide levels as low as 1 mg/L have been associated with cyanide poisonings (see Niyogi),[97] but such levels are often related to blood measurements taken after toxicity is observed or in post mortem investigations and are not reliable indications of the blood cyanide levels actually causing the toxicity.

Lambertsen[37] reported that the "minimum lethal dose of inorganic salts of cyanide is about 0.2 gm for adults." This translates to approximately 80 to 100 mg of cyanide, based on the administration of potassium or sodium cyanide. However, 1 to 6 g of the inorganic salts are usually ingested by individuals attempting suicide. Lambertsen also noted that even such high doses are not always fatal. Symptoms of acute intoxication include instantaneous collapse and respiratory arrest.[104] Other serious effects from high doses of cyanide include convulsions, paralysis, and coma.[29] The binding of cyanide to cytochrome oxidase reduces the ability of this enzyme to catalyze the use of oxygen in the critical electron-transport chain. As a result, aerobic metabolism is diminished or stopped. Histotoxic hypoxia results, first affecting the nervous system and heart.[37] Death is generally the result of respiratory arrest.[105]

EFFECTS OF CHRONIC EXPOSURE TO CYANIDE

The major health effects associated with chronic exposure to cyanide are neuropathies, goiter, and diabetes. The primary evidence linking these conditions to cyanide are reports of high incidences of these diseases in regions of high cyanide consumption, particularly regions of Africa or the Caribbean where the cyanide-containing cassava root is the staple food.[106-111] Also, reports have been made of neuropathies and goiter developing in occupationally exposed populations.[112,113] In addition, reports have been made of neuropathies primarily affecting the optic nerves of people who have been exposed to cyanide from tobacco smoke.[42,114-118]

Neuropathies

Although cyanide is probably a contributing factor in neuropathies associated with cyanogenic foods and smoking, other important factors are also causally linked to the development of the neuropathies. Most important among these are the protein and vitamin B_{12} deficiencies noted in the affected populations. Protein deficiencies produce

a shortage of the sulfur-containing amino acids that are important in the detoxification of cyanide to thiocyanate (see previous discussion of metabolism). Ingestion of small quantities of cyanide will readily deplete the body's storage of vitamin B_{12} (see previous discussion of metabolism). At least some of the demyelinating neuropathies associated with cyanide intake can be brought on by a diet lacking in vitamin B_{12}.[86,119] The importance of dietary B_{12} is further emphasized by the fact that at least some of the cyanide-associated neuropathies can be reversed in humans by administration of vitamin B_{12} supplements.[120] A rare hereditary inability to detoxify cyanide may contribute to some of the neuropathies affecting the optic nerve, as in the case of tobacco amblyopia found in some smokers.[116] Many of the neuropathies associated with chronic cyanide exposure are believed, in fact, to be the result of repeated, acute anoxias caused by exposures to high levels of cyanide.[34]

Thus, it appears that cyanide can be a contributing factor in some chronic neuropathies; however, other factors such as dietary deficiencies or hereditary sensitivity must also be present. The fact that these symptoms disappear (if caught early enough) when diet deficiencies are corrected[120,121] suggests that widespread development of the effects will not appear in an adequately nourished population, such as military personnel, that is exposed to low levels of cyanide. It also suggests that early stages of the condition are reversible.

Goiter

Goiter is another condition associated with long-term exposure to cyanide. Evidence linking cyanide and goiter include epidemiology studies showing high prevalence of goiter in regions of high levels of cyanide consumption.[122] Also, a few cases of goiter developing in occupationally exposed groups have been reported.[112,113] The effects on the thyroid appear to be the result of the metabolite thiocyanate, which inhibits the thyroid's mechanism for accumulating iodide from the plasma. Thiocyanate can also block the incorporation of iodide into organic substances, a step required in the synthesis of the hormone thyroxin.[123] Thiocyanate was previously used as an antihypertensive drug, and several cases of goiter developed from this use.[124-126]

A deficiency of dietary iodine is believed to have contributed to the occurrence of goiter in populations that consumed cyanide-containing foods.[122] In a study by El Ghawabi et al.,[112] 20 of 36 workers exposed occupationally to cyanide had mild to moderate enlargement of the thyroid. However, no correlation was found between either incidence or degree of thyroid enlargement and period of exposure, and none of the workers showed clinical signs of hypo- or hyperthyroidism.

Diabetes

Evidence exists that cyanide from the consumption of cyanide-containing foods is a causal factor in the development of malnutrition diabetes, a form of diabetes associated with diets that are low in protein.[126-128] The cyanide ion is thought to contribute to the condition by damaging critical proteins in the insulin-producing cells of the pancreas.[129] However, malnutrition is assumed not to exist for military personnel, and so this type of diabetes is not likely to occur in military populations exposed to low doses of cyanide for up to one year.

DEVELOPMENT OF RECOMMENDATIONS FOR STANDARDS

The objective of this section is to develop recommendations for establishing water-quality standards for cyanide. We begin with a discussion of the methodology we used to derive our recommended limits for cyanide in field waters. We then present our calculations and identify major uncertainties and assumptions.

METHOD AND RATIONALE

The standards recommended in this chapter are designed to prevent histotoxic anoxia caused by the intracellular accumulation of cyanide and the blocking of electron transport. Because intracellular concentrations of cyanide are difficult to measure, the more readily available measurement of cyanide concentration in whole blood is used as an indicator of the body's cyanide burden. Whole-blood concentrations are correlated with physiological effects (Table 2), and the highest blood concentration that does not produce performance degradation is the basis for the recommended standards. The concentrations of cyanide in whole blood resulting from consumption of cyanide-containing water are estimated with a pharmacokinetic model.

The model used in this document (Eq. 1) is a one-compartment pharmacokinetic model that is based on first-order absorption and elimination.[130]

$$C = \frac{f \cdot D \cdot k_a}{V_d(k_a - k_e)} \left[\frac{1 - \exp(-k_e n\,\Delta t)}{1 - \exp(-k_e\,\Delta t)} \exp(-k_e t) - \frac{1 - \exp(-k_a n\,\Delta t)}{1 - \exp(-k_a \Delta t)} \exp(-k_a t) \right] \quad (1)$$

where

- D = repetitive dose, mg;
- V_d = volume of distribution, L;
- k_a = first-order rate coefficient for absorption, min^{-1};
- k_e = first-order rate coefficient for elimination, min^{-1};
- C = contaminant concentration in blood at time t (min) after the nth administration, mg/L;
- n = number of repetitive administrations;
- Δt = time between administrations, min; and
- f = fraction of dose absorbed, dimensionless.

As explained previously, cyanide is detoxified rapidly and acute toxic reactions appear when the rate of absorption exceeds the combined rates of detoxification and excretion. Because of its rapid decay in the body and the almost immediate appearance of acute cyanide toxicity, the use of the pharmacokinetic model is the best tool for developing standards for cyanide in military field-water supplies. The usual approach of estimating an allowable daily dose by diluting the daily dose into a volume of water equal to a day's water consumption does not provide the precise, time-dependent dosing estimates needed to prevent the toxic reactions that can result from the quickly acting cyanide ion.

As discussed in the sections on metabolism and chronic health effects, chronic cyanide toxicity appears to be almost exclusively limited to malnourished populations. It is recognized that optical neuropathies may develop in a small, genetically-sensitive subpopulation that is exposed to cyanide through tobacco smoke. Chronic effects may also appear following repeated acute poisonings. However, there is no reason to expect that effects of chronic cyanide exposure will appear in an adequately nourished military population that is not subjected to repeated acute cyanide toxicity. Accordingly, the recommendation for a short-term ($\leq$7 d) cyanide standard is applicable to long-term ($\leq$1 y) exposure periods as well.

CALCULATION OF RECOMMENDATIONS FOR STANDARDS

Application of the pharmacokinetic model to the estimation of safe concentrations of CN in water was accomplished in two steps. First, we estimated values of the model parameters from data in the literature and second, we calculated cyanide doses (and the associated CN concentrations in water) that would not result in concentrations of blood cyanide that exceed safe levels.

Estimation of k_e and k_a

One important source of data on the decay of cyanide in blood is from Vesey et al.,[131] who reported CN concentrations in plasma and red blood cells for a set of patients receiving SNP infusions (SNP reduces blood pressure). From their concentration data (for measurements made at the end of infusion and one-hour post infusion) we calculated a geometric mean value (GM) of 0.012 min^{-1} for the k_e of CN in plasma (geometric standard deviation (GSD) of 2.4 and n=19) and a GM of 0.016 min^{-1} for the k_e of CN (GSD = 2.4, n=25) in red blood cells. In a separate study dealing with blood cyanide levels following SNP infusions, Bogusz et al.[100] reported blood cyanide levels following two separate administrations of SNP to a patient. We calculated an average elimination rate constant for cyanide as 0.014 min^{-1} for that patient, which is in good agreement with the values calculated from the data of Vesey et al.[131] noted above. Sylvester et al.[66] reported a rate constant for elimation of 0.0175 min^{-1} for CN in blood drawn from dogs. At the present time it is not possible to determine whether k_e should be calculated from cyanide concentrations in plasma or red blood cells. To be conservative, we have adopted the k_e calculated from the plasma data of Vesey et al.[131] The plasma-based k_e is 75% of the RBC-based k_e (i.e., 0.012/0.016), and therefore safe doses derived from the plasma k_e will be lower than those calculated from the RBC k_e.

There are no direct measurements of k_a; however, we know that orally ingested cyanide exerts its toxic effects rapidly and so the value of k_a is high relative to the rate constant for elimination. We evaluated different values of k_a through the use of the equation for calculating the time to the maximum blood cyanide concentration: $t_{max} = (\ln k_a - \ln k_e)/(k_a - k_e)$. With k_a equal to 0.2 min^{-1} and k_e equal to 0.012 min^{-1}, t_{max} is equal to about 15 min; with k_a equal to 1 min^{-1} and k_e = 0.012 min^{-1}, t_{max} equals 4.5 min. These values are consistent with reports that deaths from acute cyanide intoxication can occur within 2 to 20 minutes.[28] Part of the variation in k_a is due to the form of cyanide ingested (i.e., HCN is absorbed more rapidly than KCN, which ionizes in an aqueous solution to produce CN^- molecules that are not absorbed quickly). As a means of dealing with the uncertainty associated with this parameter, we have assumed that k_a is uniformly distributed between 0.2 and 1 min^{-1}. In other words, the values of k_a between these upper and lower bounds have an equal probablility of occurrence.

Estimation of V_d and f

The volume of distribution for cyanide in blood was estimated to be 5.25 L for a 70-kg person, which is calculated from a V_d of 75 mL/kg reported by Pasch et al.[94] A

similar value (70 mL blood/kg of body weight) has been cited by Vesey et al.[131] These values represent the volume of whole blood in typical individuals. We note, however, that the actual distribution volume of cyanide could be somewhat higher. Therefore, our value for V_d should lead to estimated doses of cyanide that are lower than expected, and consequently the associated concentrations of cyanide in field water will also be lower. The fraction of cyanide (f) administered orally that actually reaches systemic circulation in blood is more difficult to estimate because of the potential for significant first-pass detoxification in the liver subsequent to uptake from the gastrointestinal tract. As a means of determining a range of likely values for f, we computed blood cyanide levels for individuals who had taken known amounts of cyanide. This was accomplished by using alternative values of f until one yielded a level of cyanide in blood that corresponded with one at which the acute effects would be observed. The first case we used to estimate f involved an attempted suicide. The data from this incident are quite unusual because both the cyanide dose taken as well as the blood cyanide level within an hour of the initial posioning were reported (see Edwards and Thomas).[132] The individual (a chemist) carefully weighed out 413 mg of potassium cyanide (165 mg cyanide equivalent) and then swallowed that amount on an empty stomach. After the individual was admitted to a local hospital, a blood sample was analyzed for cyanide. The results of that analysis revealed a concentration of 3.8 mg/L (at approximately 60 min. post ingestion). With k_a and k_e set at values of 0.2 and 0.01 min^{-1} respectively, and V_d equal to 5.25 L (Δt was set equal to 120 min and n equal to 1 to represent the case for a single, nonrepetitive, administration), a value of f equal to 0.21 yielded a blood concentration of 3.8 mg/L at 60 min after cyanide administration. The peak blood level calculated was 5.6 mg/L, which represents a concentration that would produce severe, life-threatening symptoms. With k_a = 1 min^{-1} and k_e = 0.012 min^{-1}, f was calculated to be 0.245. In a second case of acute intoxication, which was fatal, values of f equal to 0.2 to 0.5 would have produced lethal levels of blood cyanide within 2 to 3 min in an individual who ingested 300 mg of HCN.[37] Therefore, to reflect the uncertainty in this parameter, we assume that f is uniformly distributed between 0.2 and 0.5.

Estimation of Safe Levels of Blood Cyanide

There has been much speculation regarding the levels of cyanide in blood that elicit toxic responses as well as those that are nontoxic. The most reliable data concerning safe levels of blood cyanide are from the literature reporting measured concentrations of cyanide in blood drawn from patients receiving infusions of SNP during surgery.

Vesey et al.,[131] for example, measured cyanide in red blood cells from 26 patients at concentrations as high as 20 μmol/100 mL (equivalent to about 2 mg/L in whole blood). Aitken et al.[95] measured blood cyanide levels of up to 2 mg/L in 13 patients receiving SNP infusions. Schulz et al.[96] measured cyanide levels in red blood cells in 51 patients administered SNP and found that 10 of the 51 patients had concentrations above 50 nmol/mL or about 0.5 mg/L in whole blood. Two patients had concentrations of cyanide equivalent to 1 mg/L in whole blood. In addition, they reported on a separate case of a patient who had a maximum concentration in red blood cells of 261 nmol/mL or 2.9 mg/L of cyanide in whole blood.[96] Of the 91 patients in these three studies, only one had symptoms of tissue hypoxia and that individual was reported by Aitken et al.[95] to have had a blood cyanide level of 2 mg/L.

In the study by Aitken et al.,[95] the apparent threshold for metabolic acidosis was about 0.5 mg/L of cyanide in whole blood. At levels of about 1 mg/L, detectable changes occurred in the base deficit (e.g., acid neutralizing capacity), and blood adenosine triphosphate (ATP) levels in four patients. No clinical symptoms were observed at these levels except for the patient with the highest level of blood cyanide (i.e., 2 mg/L). Based on their findings, together with the results of the other researchers noted above,[96,131] we conclude that 0.5 mg/L of cyanide in whole blood is a reasonable threshold level for changes in blood chemistry and that clinical symptoms of cyanide intoxication are likely above a concentration of approximately 2 mg/L.

Water Consumption Patterns

In order to use Eq. 1 to calculate safe doses of cyanide and associated concentrations in field water, we defined two sets of water consumption patterns for drinking 5 and 15 L of water per day. The actual consumption patterns are represented by the number of repetitive administrations (i.e., drinks of water) that occur during a day and the interval between administrations. The first scenario is based on a typical 8-h work period during which there are 60-minute intervals between drinks; the second scenario lasts 5 hours, with only 30 minutes between drinks. This latter scenario is meant to cover the case where heavy labor occurs over a few hours of time and thus more frequent drinks of water must occur to compensate for sweat losses during that period.

Model Results

Because there is considerable inter-individual variability in the pharmacokinetic parameters of cyanide as well as in the responses to different levels of blood cyanide, we

computed doses that would not exceed a blood cyanide concentration of 0.5 mg/L for different values of f, k_a, and k_e randomly selected from distributions of values representing those variables. We assumed that the values of f are uniformly distributed between 0.2 and 0.5, based on our previous analysis of the possible limits to f. We also assumed that k_a was uniformly distributed between 0.2 and 1 min^{-1} (a sensitivity analysis showed k_a did not significantly affect estimated dose estimates). Our statistical analysis of data on k_e indicated that it is lognormally distributed with a geometric mean of 0.012 min^{-1} and a geometric standard deviation of 2.4. The value V_d was held constant at 5.25 L because there were no data to support alternative values. Safe doses of cyanide that did not result in blood cyanide levels greater than 0.5 mg/L were calculated for 1000 separate Monte Carlo simulations in which values of f, k_a, and k_e were randomly selected from the respective distributions, which were assumed to be independent. The median doses and associated concentrations in water for different water consumption levels and patterns are shown in Table 3. The cyanide doses and related concentrations decrease as the period between drinks decreases because blood cyanide levels increase faster than cyanide can be detoxified via conversion to thiocyanate. One issue, therefore, with respect to a cyanide standard is whether one unusually large drink of water, for example, 3 L of water consumed within a period of several minutes, could lead to cyanide toxicity when the water contains the levels of cyanide presented in Table 3. To investigate this, we used Eq. 1 to calculate the blood levels that would result from consuming 3 L of water containing cyanide concentrations equivalent to those presented in the last column of Table 3. A dose of 21 mg of cyanide (3 L x 6.9 mg/L) would produce blood cyanide values of nearly 2 mg/L, based on a high value of f (0.5), a low value of k_e (0.005 min^{-1}), and k_a = 1 min^{-1}; with a dose of 17 mg of cyanide (3 L x 5.8 mg) the maximum blood level would not exceed 1.5 mg/L, using the same parameter values. These levels of blood cyanide are not likely to produce clinical symptoms of toxicity. However, because blood cyanide levels above 2 mg/L are apt to cause severe but reversible symptoms, we recommend that 6 mg/L of cyanide be established as an upper-bound concentration limit in water and that the maximum volume of water consumed during an hour's time be less than 3 L when cyanide is present or suspected in field waters. Our recommended limits for cyanide in field waters are 2 mg/L for water consumption of 15 L/d and 6.0 mg/L for 5 L/d of water. At these levels even sensitive members of the field personnel exposed to cyanide in their drinking water will be protected against performance-degrading effects.

Table 3. Cyanide doses and associated concentrations in water that would not lead to performance-degrading effects, for different water consumption levels and patterns.

Parameter summary: (see Eq. 1)

f is uniformly distributed between 0.2 and 0.5

k_a is uniformly distributed between 0.2 and 1 min^{-1}

k_e is lognormally distributed with a GM of 0.012 min^{-1} and a GSD of 2.4

V_d = 5.25 L

C = 0.5 mg/L (safe level of cyanide in whole blood)

Number of administrations	Dose interval Δt (min)	Cyanide dose[a] (mg)	Volume of water[b] consumed per drink (L)	Concentration of cyanide in water (mg/L)
8	60	4.3 (5.1)[c]	0.625	6.9 (8.2)[c]
8	60	4.3 (5.1)	1.875	2.3 (2.7)
10	30	2.9 (3.5)	0.5	5.8 (7.0)
10	30	2.9 (3.5)	1.5	1.9 (2.3)

[a] The geometric-mean dose of cyanide was calculated by running 1000 Monte Carlo simulations in which different values of f, k_a and k_e were randomly selected from representative probability distributions. The geometric standard deviation of the doses was 2.

[b] The volume of water consumed at each administration is calculated by dividing the daily volume (either 5 or 15 L) by the number of administrations.

[c] For comparative purposes, we also calculated geometric-mean doses (in parentheses) using k_e = 0.016 min^{-1}, the geometric mean of the k_e values of cyanide measured in red blood cells (the geometric standard deviation equals 2.4).

MAJOR UNCERTAINTIES AND ASSUMPTIONS

1. The amount of reliable data correlating the concentrations of cyanide in whole blood to health end points is small. Estimates of toxic concentrations of cyanide in whole blood are made from samples taken from humans subjected to other stresses (e.g., sodium nitroprusside, surgery, CO, diet deficiencies, and perhaps other factors). Differences involving analytic methods and the time from dosing to analysis are also important factors in explaining the variability in reported concentrations.

2. The standards, as recommended, assume that elimination of cyanide via sweat is insignificant. However, cyanide losses by this route could be substantial if the thiocyanate concentrations measured in perspiration under conditions of low sweat production are the same during periods of maximal sweat production and if they reflect actual losses of cyanide (see previous discussion of cyanide elimination). The elimination coefficient (k_e) that was used for calculating recommended standards would probably be too small where elimination via sweat is significant, and a higher cyanide concentration in drinking water might be tolerable.

3. The volume of distribution (V_d) estimate is based on the volume of whole blood in a 70-kg individual. However, as we noted, the actual volume of distribution may be somewhat higher.

RECOMMENDATIONS FOR STANDARDS

Table 4 compares the standards recommended by this study to those recommended by other military studies, the World Health Organization (WHO), and the U.S. Environmental Protection Agency (EPA). The short-term standard of 20 mg/L that is recommended in TB MED-229[133] appears to be too high for consumption rates of 5 and 15 L/d when compared to the minimum fatal dose of around 50 mg. The long-term standard of 2 mg/L in TB MED-229[133] is identical to the recommendation of this study for a 15-L/d consumption rate, but it is a factor of three lower than our recommendation for a 5-L/d rate. The QSTAG-245 recommendation[134] for short-term exposures is the same as that recommended in TB MED-229,[133] but the recommendation for long-term exposures (>7 d and assumed applicable to a period of up to 1 y) is lower than that recommended by TB MED-229 or this study.

The long-term standards recommended for cyanide in TB MED-229[133] and in the first edition of QSTAG-245[137] are ten times lower than the respective short-term standards. However, the latest edition of QSTAG-245[134] indicates that for long-term consumption (>7 d) at a rate of 5 L/d the minimum treatment requirement for cyanide is

Table 4. Comparison of recommended drinking-water standards for cyanide.

Recommended standard (mg/L)			Assumed water consumption (L/d)	Source
≤ 7 d	≤ 1 y	Unspecified exposure period		
2	2		15	Maximum concentration recommended by this study
6	6		5	Maximum concentration recommended by this study
20	2		---[a]	Military field-water-quality standard contained in TB MED 229[133]
20	0.5		5	QSTAG-245 minimum treatment requirements for assuring potability[134]
		0.05[b]	2.5	WHO, European Standards[135]
		0.05	2.5	WHO, International Standards[136]
		0.2[c]		U.S. EPA ambient water-quality criteria for cyanide[18]

[a] Water consumption rate not stated.

[b] "...grounds for rejection of piped supply."

[c] U.S. EPA criteria, based on toxicity to fish because human and animal data were insufficient to recommend a higher level.

0.5 mg/L, which is a factor of 40 lower than the minimum treatment requirement for short-term consumption (≤7 d).

The cyanide standards recommended by the WHO are based on the capabilities of treatment processes rather than health effects. Because cyanide is destroyed readily by conventional treatment processes, the WHO proposed its recommendation to ensure that the water is not too highly contaminated with industrial effluents and that treatment is adequate.[136] The U.S. EPA does not have a promulgated standard for cyanide, but an EPA criteria document[18] showed no reason to lower the old 0.2 mg/L recommendation by the U.S. Public Health Service. The basis of this recommendation, as originally proposed by the U.S. Public Health Service, is the protection of fish.[138] The U.S. EPA[18] notes that this provides a safety factor range of 41 to 2100 for human health.

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CHAPTER 9. LINDANE

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ABSTRACT

In this chapter drinking-water standards for lindane are developed and recommended. The recommended standards are intended to prevent performance-degrading or irreversible effects in troops who will be exposed to lindane-containing water for up to either 7 d or 1 y. The 7-d and 1-y standards are calculated assuming both 15-L/d and 5-L/d water-consumption rates. Uncertainties and assumptions associated with the recommended standards are identified and explained to allow maximum flexibility in administration. For an assumed daily rate of water consumption of 15 L, the recommended standard is 0.2 mg/L for an exposure period up to either 7 d or 1 y. For an assumed daily rate of water consumption of 5 L, the recommended standard is 0.6 mg/L for an exposure period up to either 7 d or 1 y.

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INTRODUCTION

The purpose of this research is to recommend the maximum concentrations of Lindane that can be tolerated in drinking water without causing performance degradation or irreversible adverse effects in military personnel. Different maximum concentrations are recommended for assumed exposure periods of up to 7 d and up to 1 y. Under each assumed exposure period, two maximum lindane concentrations are recommended: one based on water consumption of 15 L/d and the other for 5 L/d. Studies of water consumption by men performing physical labor in hot climates, and U.S. Army field experience in desert situations, indicate that 15 L is not an unreasonable amount of water to expect individuals to drink in a day. Five liters is a more reasonable expectation under less severe conditions.

First, we describe some of the chemical properties of lindane that affect its toxicity and the likelihood of its presence at toxic levels in drinking water. Second, we briefly describe some of the most common methods for measuring lindane levels in water. Third, we summarize the pharmacokinetic (i.e., absorption, distribution, metabolism, and elimination) characteristics of lindane in humans. The pharmacokinetic information selected for inclusion helps to explain some of the variability found in the toxic responses to lindane in humans and animals. A brief summary follows of the effects that lindane has produced in animals and humans following acute, subacute, and chronic exposures. The highest exposures in these studies that did not cause any effects judged to be capable of degrading performance form the basis for the recommended standards.

Finally, this document describes how the recommended standards were calculated and makes explicit the important assumptions that are incorporated into the recommendations. Making the methods and assumptions explicit should facilitate the adaptation of the recommended standards to any field situations where the assumptions made in this document might not apply. For 5- and 15-L/d water consumption rates, the recommended standards are 0.6 and 0.2 mg/L, respectively, for exposure periods up to either 7 d or 1 y. For further consideration, proposed standards for two other stereoisomers of the parent chemical of lindane are also shown and compared with available monitoring data for their occurrence in field water.

GENERAL PROPERTIES

Lindane is the common name for the gamma-isomer [Chemical Abstracts Service (CAS) Registry No. 58-89-9][1] of the chemical 1,2,3,4,5,6-hexachlorocyclohexane (HCH).

In addition to the gamma-isomer, the technical-grade HCH mixture (CAS Registry No. 608-73-1) contains seven other stereoisomers (Table 1), as well as heptachlorocyclohexane and octachlorocyclohexane. Benzene hexachloride (BHC) is also used commonly to denote the mixed isomers of 1,2,3,4,5,6-HCH.[2]

The gamma-isomer is the main insecticidal component of the HCH mixture[1,3]; and, as shown in Table 1, technical-grade HCH contains approximately 13 to 14% of the gamma-isomer. This fraction is isolated to a high degree of purity during production.[4] However, to be designated as "lindane," it must have at least 99% gamma-HCH, the remainder consisting of other HCH isomers.[1,2] Lower-concentration mixtures are referred to as concentrated, fortified, or enriched HCH. Technical grades such as these contain a mixture of several isomers that vary greatly in gamma-isomer distribution. These HCH mixtures are also used as an insecticide throughout the world.[5]

Lindane is known worldwide by several other names. Some of the most commonly used names are Gamaphex, gamma-HCH, Gamma-BHC, Gammalin, Gammex, Isotox, Lindafor, Lintox, Nexit, Novigam, Silvanol, Agromexit, Gammexane, Exagama, Forlin, Gallogama, Inexit, Lindagam, Lindagrain, Lindagramox, Lindalo, Lindamul, Lindapoudre, and Lindaterra.[1,6,7]

Lindane is a colorless solid with a slightly musty odor, a melting point of 112 to 113°C, and a vapor pressure of 9.4×10^{-6} mm Hg at 20°C.[1,7,8] Solubilities reported in organic solvents at 20°C are acetone, 435 g/L; benzene, 289 g/L; chloroform, 240 g/L; diethyl ether, 208 g/L; and ethanol, 208 g/L.[8] It is slightly soluble in water, with reported solubilities of 7.3 to 10 ppm at 20 to 25°C, 12.0 ppm at 35°C, and 14.0 ppm at 45°C.[1,7] It has a log octanol/water partition coefficient of 3.72[9] and an odor-threshold detection level of 12.0 ppm.[10]

Lindane is used widely as an agricultural and household insecticide, scabicide, pediculicide, parasiticide, and in baits for rodent control.[1,9] As an insecticide, it is effective against soil-dwelling and plant-eating insects found on fruit, rice, cereal, vegetable, sugarcane, sugar-beet, oil-seed, and cotton crops.[1,6,11] As such, it is likely to be encountered any place in the world. Lindane is also used as a public health measure against the mosquito vector of malaria and the triatomid vectors (reduviid bugs) that transmit Chagas' disease.[7,12,13]

Lindane is reported to be moderately persistent in natural water, with a half-life of 6 to 25 wk.[14] Biodegradation/ biotransformation appears to be the most important process involved in the degradation of lindane in the aquatic environment.[15] Recent results indicate that hydrolysis and sorption are also important processes.[9] Photolysis

Table 1. Stereoisomers of technical-grade HCH mixture.[a]

Isomer	Approximate % in technical-grade HCH	CAS Registry No.
Alpha	65	[319-84-6]
Beta	11	[319-85-7]
Gamma	13-14	[58-89-9]
Delta	8-9	[319-86-8]
Epsilon	3-5	[6108-10-7]
Eta	--	None
Theta, zeta	--	None
HCH mixture	100	[608-73-1]

[a] Source: Worthing[1] and U.S. EPA.[2]

may also be a degradative pathway in alkaline water of pH 9.[9] Volatilization and oxidation, however, do not appear to be significant factors in the breakdown of lindane.[15]

Lindane is believed to enter water systems via rainfall, runoff, leaching, direct application for mosquito control, or from its use on rice.[13,16-18] Because lindane is adsorbed by upper soil layers, it does not appear that significant amounts of lindane reach the water by runoff or leaching.[16] However, since lindane has been known to persist in soil for 10 y or more (95% disappears in 3 to 10 y), the possibility of its presence in a soil environment should be noted.[19]

OCCURRENCE

Lindane has been found in a variety of waters throughout the world (see Table 2). Most of the reported occurrences were in samples of surface waters, primarily rivers. Levels up to 2.0 µg/L were detected occasionally in surface waters, but most values were well below 1.0 µg/L. The only significant concentrations of lindane in water were detected in rice-paddy water in Iran[17] (1920 µg/L) and in canal water in Germany (7.1 µg/L).[33] However, concentrations at or near these levels have been measured only

Table 2. Reported lindane concentrations in various waters worldwide.[a]

Total lindane level (µg/L)	Type of water	Ref.
0.000	River water, India	20
0.000	Groundwater, Israel	21
0.000	Pond water, India	20
0.000	Lake water, Kenya	22
0.000	Ocean, Atlantic, U.S.	23
0.0002	Ocean, Antarctic	24
0.009	River water, Argentina	25
0.119	River water, Israel	26
0.179	River water, Japan	27
0.290	Tap water, Egypt	28
0.295	Ocean, France	29
1.170	Groundwater, Egypt	30
1.600	River water, Norway	31
2.090	Lake water, Egypt	32
7.100	Canal water, West Germany	33
1920.0	Paddy water, Iran	17

[a] Based on detectability limits of analytical equipment employed at the time that lindane concentration in water sample was determined.

in water near agricultural activities. Water samples from Israel and Egypt also contained only low levels of lindane, occasionally reaching levels up to 2.09 µg/L.[21,30,32]

METHODS FOR DETECTION OF LINDANE

The fastest, simplest, and most sensitive method for detecting lindane is gas chromatography,[34-36] where determination of quantities in the microgram-per-liter range (µg/L) is possible. Further confirmation of lindane by a quantitative technique such as mass spectrometry is recommended,[37,38] although equipment for such analysis

is probably not available for military field operations. Currently, there does not appear to be a detection method for lindane or any of the other isomers of HCH that is approved by the Army.[39]

PHARMACOKINETICS

The pharmacokinetic processes are important in determining the toxic response to any chemical. Lindane and other HCH isomers are thought to be absorbed from the gastrointestinal tract, distributed in the body, metabolized (detoxified), and eliminated. In addition, some of the factors that alter the pharmacokinetics of HCH isomers may explain some of the variability reported in human and animal responses to HCH.

ABSORPTION

The absorption of lindane from the intestinal tract appears to be rapid and complete. The mechanism by which lindane is absorbed is not well understood, but Turner and Shanks found evidence suggesting that lindane is not absorbed into the lymphatic system to any appreciable extent; it appears to be absorbed directly into the blood.[40] The importance of this is that it is passed through the liver and undergoes substantial detoxification before being distributed further throughout the body.

Albro and Thomas studied the extent to which various HCH isomers were absorbed from the gastrointestinal tract of rats.[41] The technical-grade HCH was mixed into cottonseed oil and administered by stomach tube for a single-dose experiment. For a 14-d experiment, the HCH was mixed into rat chow that the animals ate ad lib. In the single-dose experiment, an average of 95.8% of the administered dose was "removed" from the intestinal tract within 96 h after dosing. Varying the HCH dose between 30 and 125 mg/kg (of body weight) did not affect the absorbed fraction, nor was any difference found between the alpha-, beta-, and gamma-isomers. In the 14-d study, an average of 94.9% of the technical HCH was "removed". Unlike the single-dose experiment, a difference was found in the extent of absorption of the isomers. The gamma-isomer was absorbed most (99.4%), and the beta-isomer was absorbed least (90.7%). At the end of the 14-d period, no HCH was detected in the bile, suggesting that the excreted HCH actually represented HCH that was never absorbed rather than representing HCH that had been absorbed and then excreted, unmetabolized, back into the digestive tract via bile.[41]

To evaluate how rapidly lindane is absorbed from the gastrointestinal tract of mice, Abdaya et al. administered ^{14}C-labeled lindane in a carrier (Emulphor:ethanol:water, 1:1:8) by gavage.[42] Each mouse received a lindane dose of 1 mg/kg (of body weight). Within 1 min after dosing, 14.2% of the lindane was absorbed into the body; in 60 min, 70.7% was absorbed. The time for 50% of the lindane in the gut to be absorbed ($T_{0.5}$) was estimated to be 14.2 min. For comparison, the $T_{0.5}$ values estimated for two other organochlorine compounds, DDT and dieldrin, were 62.3 and 42.1 min, respectively. The range determined for three carbamates was similar to that of lindane, 10.0 to 17.0 min, and the range for four organophosphates was 23.5 to 78.1 min.

Experiments by Turner and Shanks also indicated that lindane is absorbed rapidly from the gut.[40] They injected 50 and 100 nanomoles of lindane in 0.4 mL of rat bile into rat intestinal loops. Among the animals injected with 50 nanomoles, an average of 37.7% of the lindane was absorbed within 30 min. This absorption was higher than the corresponding findings for DDT (4.4%) and hexachlorobenzene (8.4%). When 100 nanomoles were injected, the percentages absorbed within 30 min were 47.6, 9.6, and 2.3 for lindane, hexachlorobenzene, and DDT, respectively.

One potentially important variable in the absorption studies and in the toxicity studies is the carrier used to deliver lindane or other HCH isomers. Herbst and Bodenstein listed several LD_{50} (lethal dose to 50% of population) values for a variety of species, including dog, cat, and rodents, that were determined by various researchers using different carriers.[43] A comparison of these results indicates that the carrier influences the toxicity of the HCH, presumably by influencing the absorption. Muralidhara et al. investigated the importance of this factor by intubating female rats with 125 mg lindane/kg of body weight in various carriers and comparing mortality.[44] They used a 125-mg/kg dose because this was the acute oral LD_{50} when Durobase oil was the carrier. (Durobase oil is a mixture of vegetable and mineral oils including ground-nut [peanut], castor, and jute-batching oils.) Delivering the lindane in either peanut oil or coconut oil raised the mortality to 70%. The observed mortality was reduced to 20% with olive oil, 10% with cottonseed oil, and 0% with castor oil. With SAE-30 mineral oil, mortality was 10%; no mortalities resulted with SAE-90 oil as the carrier. Water was also tested, and it produced 10% mortality.[44] Unfortunately, one of the most commonly used carriers in toxicity studies, corn oil, was not evaluated.

No direct evidence was found of the extent or rate at which lindane is absorbed when delivered in drinking water. However, Muralidhara et al. observed the same mortality rates when cottonseed oil or water was used as the carrier.[44] Thus, it appears prudent to assume that absorption from water is no less extensive or less rapid than it is from cottonseed oil. In addition, Albro and Thomas showed that absorption of doses of up to

125 mg/kg of body weight were almost completely (95%) absorbed when cottonseed oil was the carrier.[41] Thus, for the practical purpose of establishing a drinking-water standard, it also appears reasonable to assume that absorption of lindane from consumed water will be complete (i.e., 100%).

It is interesting to compare the 10% mortality that occurred when cottonseed oil was the carrier, with the 70% mortality observed when peanut oil or coconut oil was the carrier.[44] Because absorption is 95% complete when cottonseed oil is used,[41] some factor other than completeness of absorption could be involved to explain the difference in observed mortality. This factor has not been determined in these studies, but it could be faster absorption rates or synergism.

Lindane also can be absorbed through the skin. Human studies demonstrating this fact include one by Feldmann and Maibach in which an average of 9.3% of a dose was recovered in the urine after an acetone solution of lindane had been applied to the forearm.[45] Because treatment for scabies includes the application of 1% lindane in acetone solution to the skin, extensive clinical experience with topical lindane application has been gained. In one study, Ginsburg et al. applied a 1% solution of lindane to virtually entire bodies of children and measured the resulting concentrations of lindane in their blood.[46] Maximum concentrations of 0.028 mg/L in the scabies-infected group and 0.024 mg/L in the noninfected group were attained in about 6 h.

In summary, the limited amount of information available suggests that lindane and other HCH isomers can be absorbed rapidly and completely from the intestine. Differences in mortality rates and toxicity suggest that the carrier is an important variable. The reason for this is not clear but may result from some carriers inhibiting absorption or otherwise influencing the rate of absorption. Because of the importance of the carrier, it is difficult to extrapolate dose-response data from doses delivered in oil to situations where lindane will be consumed in water. Nevertheless, for the purpose of deriving recommended field-water-quality standards, we assume that all HCH consumed in drinking water will be absorbed.

DISTRIBUTION

Lindane and other HCH isomers are distributed primarily to adipose tissues, but they can be found also in kidney, brain, liver, and muscle tissues.[47-51] To gain a better understanding of the nervous-system effects of HCH isomers, many researchers have investigated the distribution of HCH isomers in the central nervous system (CNS).[48,52,53]

Sedlak showed that the different equilibrium storage levels of the HCH isomers in abdominal adipose tissue of rats cannot be explained by differences in solubilities of the various isomers in rat fat.[54]

Frawley and Fitzhugh showed that lindane disappears from fat tissues of rats faster than alpha-, beta-, or delta-isomers.[55] Rats that were fed a diet containing 100 mg lindane/kg of body weight accumulated a lindane concentration of 102 mg/kg in their fat. After one week of a control diet (i.e., containing no HCH), no lindane was found in the fat. Rats that were fed a diet containing 100 mg beta-HCH/kg of body weight accumulated in their fat a beta-HCH concentration of 1014 mg/kg of body weight. After one week of a control diet, the beta-HCH concentration had only fallen to 860 mg/kg; after 2 wk, it was at 837 mg/kg. Among the four HCH isomers tested, the beta-isomer was the slowest to disappear from fat stores.[55] Lehman presented data showing that lindane disappeared from fat much faster than did DDT.[56]

Studies of HCH levels in the serum of lindane manufacturing workers also suggest that the gamma-isomer (lindane) does not continue to accumulate over long exposures, but that the beta-isomer does. Milby et al. found that blood levels of lindane increased with higher intensity of exposure but did not increase with duration of exposure.[57] When Baumann et al. measured the levels of HCH isomers in the blood of lindane manufacturing workers, they found a significant correlation between time of employment and beta-HCH levels.[58] The tendency of the beta-isomer to accumulate to a greater extent than any of the other HCH isomers may be related to the observation that it is the most toxic isomer in chronic exposure studies.[59] Similarly, the lack of long-term accumulation of lindane is probably related to its lower chronic toxicity.

METABOLISM

Isomers of HCH are metabolized to chlorinated phenols and, to a lesser extent, chlorinated benzenes. These products are then eliminated either as free phenols or benzenes or are conjugated with glucuronic acid, sulfuric acid, or glutathione.[60-66] A complete, widely accepted scheme identifying all intermediate steps and final metabolites has not been established.[13,67] Several studies have demonstrated that hepatic microsomal monooxygenases catalyze the initial steps in HCH metabolism.[68-70]

Engst et al. compared the toxicity (LD_{50}) of lindane to several metabolites of lindane.[67] They noted that the first intermediate metabolite that formed was substantially less acutely toxic than lindane itself and that most subsequent metabolites were also less toxic than lindane. Vohland et al. found three hydrophobic metabolites of

lindane in the brain tissue of rats.[53] Doses of up to 800 mg of the metabolite (3,6/4,5-1,2,3,4,5,6-hexachlorocyclohexene-1)*/kg of body weight, found in the highest concentration produced no noticeable behavioral effect in rats being studied for the neuropharmacological effects of the compound.[53] Because the toxicity of the metabolites is generally less than that of lindane itself, and because the water solubility and rate of excretion of the metabolites are enhanced, the net effect of metabolism is considered generally to be detoxification.[67]

ELIMINATION

Metabolites and unchanged isomers of HCH have been detected in the urine of animals[41,50,60,71-75] and humans.[45,63,76] In other studies, researchers have looked for metabolites or unchanged HCH isomers in the feces. Among these researchers, Engst et al. gave 8 mg lindane/kg of body weight by gavage to rats and reported that either limited metabolism of lindane was evident in the intestine or that the metabolites were absorbed completely.[72] Only lindane was detected in the feces. Koransky et al. gave lindane (40 mg/kg) intraperitoneally to rats and were unable to detect any unchanged lindane in the feces.[50] Following the accidental ingestion of a lindane pellet by a 2-1/2-y-old girl, a high level of lindane (4870 mg/kg) was found in the first fecal sample.[76] In the second sample, however, lindane could not be detected above 10 mg/kg. When the authors gave an intraperitoneal (i.p.) dose of alpha-HCH to rats, 10% of the administered dose was recovered from the feces as unchanged alpha-HCH.[50] Albro and Thomas orally administered technical-grade HCH to rats.[41] Ninety-six hours after a single dose in cottonseed oil, no intact HCH could be detected in the feces. During a 14-d period, in which rats were fed a diet containing technical-grade HCH, 5.1% of the dose was excreted in the feces as unchanged HCH isomers. However, on the 14th day, no HCH could be detected in the bile.

Feldmann and Maibach intravenously injected ^{14}C-labeled lindane into humans.[45] Within 24 h, 10.3% of the administered radioactivity was recovered from the urine; by the fifth day, 24.6% was recovered. No measurement of feces was made. Kurihara and Nakajima gave mice i.p. injections of the alpha-, beta-, and gamma-isomers of ^{14}C-labeled HCH.[74] At the end of 3 d, 57% of the radioactivity from the gamma-isomer

* Refers to a configurational isomer in which the chlorine atoms at positions 3 and 6 are above the plane of the cyclohexene ring, and the ones at positions 4 and 5 are below the ring.

(lindane) was recovered in the urine. Recoveries for the alpha- and beta-isomers were 37 and 10%, respectively. Kalra and Chawla[77] and Moubry et al.[78] showed that HCH can be eliminated with milk.

Although data documenting the relative importance of various elimination routes are limited, it appears that excretion of urine by the kidney is the primary route of elimination for HCH. The data of Kurihara and Nakajima,[74] showing that the gamma-isomer is the most rapidly excreted and that the beta-isomer is the most slowly excreted isomer, are consistent with other studies (see discussion of distribution) showing that the gamma-isomer does not accumulate and that the beta-isomer does accumulate.

HEALTH EFFECTS

Lindane (i.e., gamma-HCH) appears to be the most toxic isomer in tests for acute toxicity but the least toxic in tests for chronic toxicity. Several animal studies have been made on the chronic toxicity of lindane, but few human studies could be found. Consequently, the discussion of chronic toxicity focuses on animal studies.

ACUTE EFFECTS

A variety of symptoms have been reported following the ingestion of gamma-HCH (lindane) and technical-grade HCH. With increasing dose, the reported symptoms include a burning sensation of the tongue, nausea, dizziness, restlessness, frontal headaches, vomiting, upper abdominal pain accompanied by diarrhea, enhanced urination, increased or decreased heart and respiration rate, muscle fasciculation, equilibrium disorders, tremors, ataxia, and reflex slowing or loss.[43,79,80] At higher doses, severe epileptiform seizures can occur,[76] as well as acute renal failure and pancreatitis,[81] followed by eventual central respiratory failure and acute cardiovascular collapse, stupor, confusion, metabolic acidosis, coma, and death.[81,82]

Previously, lindane was being evaluated as a treatment for intestinal worms, and several clinical trials were conducted to find a safe therapeutic dose for humans. In one of these studies, Klosa exposed a group of nine men and women, aged 18 to 56, to HCH in varying doses and gamma-HCH content.[79] Apparently only one person was exposed to each treatment. Klosa's trials indicated that less-refined HCH can produce undesirable reactions at doses lower than the highly purified gamma-HCH. As shown in Table 3, doses with 40 and 100 mg/d of 99% lindane (gamma-HCH) did not produce any adverse effects during a 2-wk exposure period. When the dose was increased to 180 mg/d, diarrhea developed. In contrast, 40 mg/d of the technical-grade HCH with 10 to 30% lindane

Table 3. Results of human ingestion of HCH with varying gamma-isomer content.[a]

Dose (mg/d)	Exposure time (d)	Lindane content of solid formulation	Response
40	8	Refined technical-grade HCH, 10–30% lindane	Diarrhea, burning sensation on tongue
70	10	Refined technical-grade HCH, 10–30% lindane	Dizziness, nausea, light headaches; normal blood and urine analysis
40	10	Enriched HCH, 25–60% lindane	No effects
90	5	Enriched HCH, 25–60% lindane	Dizziness, diarrhea, light headaches; normal blood and urine analysis
40	14	Highly enriched HCH, 60–85% lindane	No effects
110	6	Highly enriched HCH, 60–85% lindane	Diarrhea
40	14	99% lindane	No effects
100	14	99% lindane	No effects; normal blood analysis
180	14	99% lindane	Diarrhea

[a] Source: Klosa.[79]

content produced diarrhea after 8 d of exposure. At 70 mg/d, dizziness, nausea, and light headaches appeared. No effort was made in this study to correlate extent or rate of lindane absorption with response.

Klosa administered the HCH preparations in a solid form.[79] The subjects who were ingesting preparations with less than 60% lindane reported a burning sensation on the tongue. In some cases, the sensation persisted for several hours and was reported to be intensified greatly by the consumption of hot drinks. Pain and inflammation of the mouth were also reported in some of the cases of accidental HCH ingestion.[83,84]

In another clinical study, Graeve and Hermring conducted two series of experiments on humans.[80] In the first series, 20 subjects each took three daily doses of 45 mg of pure lindane (gamma-HCH). The administered formulation was described as an emulsion of

pure gamma-HCH in a lipoid base. The emulsion was prepared in the laboratory by shaking. This preparation produced no adverse effects in any of the 20 subjects who took the preparation for 3 d. The authors also noted that in a "self-experiment" with increasing doses, amounts up to double the dose (90 mg/d) prescribed for the test subjects was "well accepted."[80]

Fifteen patients participated in a second series of experiments in which three daily doses, totaling 45 mg/d of pure lindane, were administered to each patient for 3 d.[80] This time, however, additional emulsifiers were added, and the emulsion was machine-prepared. This was done to increase dispersion and absorption of the lindane. Two patients took the prescribed dose and developed no signs of an adverse reaction. However, after ingesting a dose of 45 mg, a third patient, who was hospitalized for intestinal worms, developed epileptiform convulsions. These convulsions lasted about 10 min and were followed by nausea, vomiting, and exhaustion.

In response to this unexpected reaction, Graeve and Hermring stopped the experiment, reduced the lipid level of the vehicle, and reduced the lindane dose to two thirds of the originally prescribed dose.[80] In spite of this, a second patient developed similar convulsions, nausea, and vomiting on the third day of treatment. It was later discovered that this patient had been taking more than his prescribed dose. Four more patients also developed adverse symptoms. Three suffered nausea, stomach pains, or diarrhea; the fourth complained of dizziness and vision problems. No adverse reactions were reported for the remaining seven patients who had received the reduced dosage. Graeve and Hermring speculated that the use of the machine-made emulsion in the second series of experiments may have accounted for the dramatically different results from those seen in the first series of experiments.[80]

The literature contains many reports of acute intoxications of humans following ingestion of lindane and technical-grade HCH. One of the most notable aspects of these reports is the extent to which the range of doses reported to have no adverse effect overlaps into the range of doses reported to produce serious toxicity and fatality. For example, based on an early "self-experiment," Velbinger[85] reported that 16 to 18 mg/kg of Gammexane (gamma-HCH) in an oily solution was safe. This report is in contrast to the reports in Table 4 in which doses of 0.64 and approximately 8 to 9 mg/kg produced severe acute intoxications. The reasons for the apparent inconsistencies may be attributable to several factors, including differences in the gamma-HCH content, effects of impurities, formulation of the HCH, variability in the susceptibility of individuals, as well as other factors.[79,80] In addition, accurate estimates of dose are rare in the reports of accidental ingestion.

Herbst and Bodenstein reviewed the literature on acute lindane toxicity and concluded that 10 to 20 mg/kg of body weight is the acute lethal oral dose of lindane in humans.[43] There are many reports of people surviving much higher doses (Table 4), but these patients received medical treatment soon after ingestion of the lindane. One notable example is a case reported by Herbst and Bodenstein[91] in which a 63-kg male survived a dose of about 309 mg/kg, even though he received no medical attention until 24 h following the ingestion. The subject apparently had suffered violent convulsions and was in a deep stupor when found.

The reports of human exposure to lindane suggest that low doses can be ingested without producing clinically observable signs of poisoning. However, animal studies indicate that low doses of lindane may produce subclinical and potentially performance-degrading effects in the nervous system. For example, cats exposed to subconvulsant doses of lindane exhibited enhanced CNS responses following sensory stimulation; cortical motor outflow was enhanced three- to fivefold following sensory input.[93] In similar experiments, Woolley and Zimmer[94] and Woolley et al.[95] electrically stimulated the prepyriform cortex portion of rat brains and measured the response in the dentate gyrus. The amplitude of the evoked potential was increased even in rats that did not exhibit seizures following lindane dosing (30 mg/kg). The maximum potentiation averaged about twofold, and the potentiation of response lasted up to 2 wk in some of the rats.[95] These measurements are consistent with observations in other studies of hyperexcitability following lindane exposure.[83,90,96]

Animal studies also indicate that subconvulsant doses of lindane can increase susceptibility to CNS seizures. Excitation from sources that do not normally induce convulsions (e.g., visual, auditory, or somatosensory stimulation) may induce convulsions in lindane-treated animals.[93,97] For example, Hulth et al.[97] reported the onset of seizures in lindane-treated rabbits during stimulation with a stroboscopic light or during copulation. Pretreatment of animals with lindane also increased their susceptibility to CNS seizures following a dose of pentylenetetrazol[97] (pentylenetetrazol is used frequently as an aid to activate latent epileptic foci).[98]

Desi studied the effects of lindane doses between 2.5 and 50 mg/kg of body weight fed to rats on maze running and operant conditioning.[99] Desi's findings indicate that at the lower doses of 2.5 and 5.0 mg/kg, operant conditioning and maze running, respectively, were mildly affected. Desi also reported that these low doses and even the highest dose (50 mg/kg) did not interfere with liver function or produce histopathological changes. The lindane-treated rats also were reported to be more irritable than the controls, and the performance of the rats in the lever-pushing task (operant conditioning) was still significantly different from that of the controls 3 wk after the end of lindane treatment.

Table 4. Case reports of severe acute toxicity following lindane ingestion by humans.

Single oral dose (mg/kg)	Subject	Formulation	Response	Ref.
0.64	Male, 26 y old	Well-dispersed oily emulsion	Epileptiform convulsions, nausea, vomiting	80
8–9	11 adults, 18–52 y old	Solid gamma-HCH in coffee	Vomiting, convulsions, cyanosis, liver enlargement (2/11), residual hepatitis (1/11)	86
10–20	Adults	Unspecified	Lethal range	43
55–60	Boy, 16 y old	1% lindane shampoo	Status epilepticus,[a] reflex loss	87
65	Girl, 2 y old,	1 pill of Jacutin[b]	Acute toxic effects: vomiting, weight loss, convulsions, dilated pupils, reflex loss	88
105	Child, 2.5 y old, 14 kg wt,	2 pellets 95% gamma-HCH	Severe epileptiform seizures	76
150	Male adult	Solid gamma-HCH	Nervousness, convulsions, disturbed coordination	89
150	Adult	Unspecified	fatal	90
309[c]	Male, 63 kg	25.5% lindane emulsion	Severe convulsions, stupor, confusion, enlarged liver, no peripheral reflexes, metabolic acidosis	91
400	Adult	Technical-grade HCH	fatal	92

[a] Rapid succession of epileptic attacks without regaining consciousness during the intervals.

[b] Jacutin appears to be essentially pure lindane.

[c] Unlike other severe, nonfatal intoxications in this table, this patient did not receive medical attention immediately after intoxication.

In spite of the fact that two human studies specifically attempted to identify a dose of lindane that could be ingested over a short period of time with no adverse effects, no such dose has been clearly demonstrated. This is attributed to apparently conflicting test results. As previously described, Klosa found that 40 mg/d of solid lindane produced no adverse effects in one individual after 2 wk of exposure, and that another individual tolerated 100 mg/d for 2 wk, also with no adverse effects.[79] Graeve and Herrming found that 45 mg/d of lindane in an oily emulsion produced no adverse effects in a group of 20 patients after 3 d.[80] However, when they attempted to repeat this experiment, Graeve and Herrming found that 6 of 15 patients became ill at dose levels of 30 to 45 mg/d. One patient suffered convulsions after a dose of 45 mg, corresponding to about 0.64 mg/kg.[80] In Graeve and Herrming's second trial, the lipid content and method of mixing the lindane formulation were changed, and this may have affected the different outcomes between the two trials. Animal studies have shown that the carrier used in the administration can substantially affect the toxic response, although it is not known why (see previous discussion of pharmacokinetics).

The reports summarized in this discussion also show that higher doses of lindane can produce severe effects. A dose of lindane (gamma-BHC) in crystalline form and estimated to be between 8 and 10 mg/kg of body weight was ingested by 11 adults after accidentally being added to coffee in place of sugar and this dose produced severe intoxication in all 11 individuals.[13,43] Doses only slightly above this (10 to 20 mg/kg) can be fatal, but doses of up to 300 mg/kg have been survived with therapy.[43] Thus, it can be seen that characterizing a dose-response function for short-term exposure to lindane, including the identification of a no-effects level, is very difficult. This is, at least in part, due to (1) the fact that the reported incidents and experiments have involved a variety of carriers, and carriers appear to substantially influence toxicity; (2) an apparently large amount of individual variability in response to lindane; and (3) rough dose estimates in some cases.

CHRONIC EFFECTS

Several case reports and epidemiological studies have shown that long-term exposure to lindane can produce health effects in humans. These include studies of people exposed to lindane in the workplace (Table 5) and reports of the effects seen in people who ate food contaminated with lindane (Table 6). Unfortunately, the epidemiology studies and case reports do not include accurate estimates of exposure levels. Accordingly, animal studies must be used for dose-response estimates, and discussion of a few pertinent animal studies follows the discussion of the human studies.

Table 5. Health effects observed in populations occupationally exposed to HCH for long periods.

Exposure conditions	Exposure period	Number of exposed individuals examined	Health effects	Ref.
Lindane production factory	1 to 30 y	60	No effects on CNS or peripheral motor nerves; minor differences in blood-cell count and blood chemistry.	100,101
Lindane production factory	Few weeks to many years	40	Minor differences in blood-cell count, but within normal range.	102,103
Lindane formulation plant	0.5 to 2 y	37	Abnormal EEG in 15 of 17 workers with blood levels >20 μg/L.	104
Chemical plant: HCH, DDT, and benzilan present	1 month to 20 y	73	Clinical neurological exams all normal; mild, nonspecific diffuse changes in EEG pattern in 21.9% of exposed group.	105

Table 6. Health effects observed in populations ingesting unknown quantities of HCH in contaminated grain for long periods.

Exposure period	Number of exposed individuals examined	Health effects	Ref.
"Prolonged"	150	Mild and severe nervous system effects including seizures and death.	83
0.5 - 1 y[a]	12	Mild and severe nervous system effects, including seizures and death.	106
2 y	190[b]	Convulsive fits.	107
6 - 9 mo[c]	8	Grand mal seizures.	108

[a] Grain was also contaminated with aldrin.

[b] Actual number of individuals examined was not specified, but it appears to be at least this number.

[c] Based on period during which seizures were reported to occur.

Part of the difficulty in interpreting and comparing the results from the occupational studies is that workers were exposed to a mixture of chemicals, and that the mixture was not the same in all studies.

Exposure was by inhalation and, in at least some of the workers, by direct skin contact. Two of the studied groups listed in Table 5 worked in factories that manufactured lindane. This process involves the production of mixed-HCH isomers followed by the separation of the gamma-isomer, lindane. A methanol extraction step is used in this process. Thus, workers in lindane production can be exposed to pure lindane, mixed-HCH isomers, methanol, and to unreacted benzene in the mixed-HCH isomers.[58] The extent of exposure to these different substances depends on which step of the production process the workers are involved with and whether their functions involve skin contact with the HCH. Baumann et al. showed that the serum concentration of the alpha-, beta-, and gamma-isomers varied with assigned work stations.[58] Milby et al. measured the concentration of lindane in the whole blood of workers assigned to the same workroom (i.e., same inhalation exposure).[57] They found that the blood of the workers whose job functions required skin contact with lindane had lindane levels six to ten times higher than the blood levels of workers at the same work stations but whose job function did not involve skin contact.

The third study listed in Table 5 involved a group of workers in a factory that mixed lindane with fertilizer, and lindane was the only toxic agent reported to be present at the time of the study.[104] The fourth study in this table was conducted on a group of workers engaged in the manufacture of chlorinated hydrocarbon pesticides and with continuous exposure to HCH, DDT, and benzilan.[105]

The two groups of lindane manufacturing workers underwent some clinical laboratory tests, results of which (e.g., reduced blood creatinine, elevated polymorphonuclear leukocytes, etc.) were different from tests on control populations.[100,102,103] While there were statistical differences between the control and exposed groups, the clinical measurements were still considered to be within the range of normal physiology.[101,102] One group was given a series of tests of neurophysiological and neuromuscular function and were found to have no signs of impaired function.[100] For example, Czegledi-Janko and Avar[104] took EEG readings on workers who had been exposed to lindane for up to 2 y. They found nonspecific abnormalities in 15 of 17 workers whose blood contained more than 20 µg/L of lindane. The authors stated that EEG readings with the same type and degree of abnormalities can be found in 10 to 20% of the general population. Clinical examination of the same group of 17 workers revealed minor symptoms in 11 of the workers, and one had more serious symptoms, such as muscular jerking and emotional changes. Of 20 workers with blood levels below 20 µg/L, one had an

abnormal EEG and three had minor clinical symptoms. The mean blood concentration of lindane in a control population of workers who were not exposed to lindane in their work environments was 8 μg/L (range 3 to 17 μg/L), and none of these people had any clinical symptoms.

It should be noted that although lindane was the only toxic agent reported to be present at the time of the study, six of the workers had suffered acute aldrin poisoning 2 y previous to their examination by Czegledi-Janko and Avar.[104] The authors also noted that prior to lindane exposure in this study, EEG measurements were made on seven of the workers whose lindane blood levels exceeded 20 μg/L. The EEG measurements were normal. Five of the seven had abnormal readings following their occupational lindane exposure. The authors stated their belief that the EEG readings before and after lindane exposure supported the hypothesis that the abnormal EEG readings were attributable to the lindane exposure and not to the previous aldrin exposure.[104]

Mayersdorf and Israeli[105] gave neurological examinations to 73 workers that had been exposed to the chlorinated hydrocarbon insecticides: lindane, DDT, and benzilan. They also took EEG readings on the workers. The results of the neurological examinations were normal in all workers, but 21.9% (16/73) of the exposed workers had abnormal EEG's. The EEG recordings were similar to those made by Czegledi-Janko and Avar[104] and were described as mild, nonspecific, diffuse changes.[105]

In addition to the reports of occupationally exposed groups, there are reports of the ingestion of HCH as a result of the practice of mixing HCH with grain to protect it against insects. As shown in Table 6, consumption of the HCH-contaminated grain produced severe neurological effects, including seizures and death. These generalized seizures, myoclonic jerking of extremities, and other neurological symptoms are the same as described earlier for acute intoxications. Nag et al. reported that during the exposure period, before the cause of the seizures was ascertained, individuals suffered seizures as infrequently as one time during a 5- to 10-mo period to as often as 3 to 4 times a day for up to 10 mo.[108] A subsidence of seizure frequency and improvement in EEG findings was reported by Gupta[106] and Khare et al.[83] within 2 to 4 wk after discontinuation of the HCH-contaminated grain in the diet. During the recovery period, the patients were also given anticonvulsant drugs. Although improvements were apparent in patients with nonfatal poisonings, the patients were not observed long enough to determine whether or not they suffered any irreversible effects.

These studies indicate that prolonged exposure to lindane can produce adverse effects in humans. Because exposures in the occupational studies included other chemicals, it cannot be stated with certainty that all of the observed effects were caused

by mixed HCH or lindane. The reports of effects following prolonged consumption of contaminated grain in India provide more convincing evidence that long-term exposure to HCH can produce severe effects in humans. It should also be noted that in at least some of the cases, serious illnesses, including seizures, had a sudden onset.[83] Mild signs or symptoms apparently did not warn that overexposure to HCH was occurring.

Animal Studies

While the epidemiology studies and case reports indicated that prolonged exposure to lindane can produce serious human health effects, they did not characterize exposure well enough to construct a dose-response curve or to estimate a no-adverse-effects level. Therefore, the estimation of a no-effect dose must be based on observations from animal studies. Two animal studies reported what appears to be the lowest no-observable-effects level (NOEL) from long-term feeding exposures (Table 7). One of these studies, which was reported by Herbst, was a 1954 study of Truhaut that involved rats fed a diet containing lindane.[109] When rats of one group were fed 25 ppm, they developed no observable symptoms; however, at 50 ppm, another group developed liver hypertrophy.[109] In another study, beagles were given lindane in their diet for 2 y. No adverse effects were observed in the groups of dogs consuming diets of 25 or 50 ppm of lindane, but the groups consuming diets of 100 or 200 ppm developed dark, friable (easily reduced to powder), slightly enlarged livers and elevated levels of serum alkaline phosphatase.[47] Based on these two studies, the World Health Organization/Food and Agriculture Organization (WHO/FAO) estimated the NOEL to be 1 mg/kg of body weight.[12] The acceptable daily intake of 0.01 mg/kg of body weight was calculated by dividing the NOEL by a safety factor of 100.[110]

In another lifetime feeding study using rats, no adverse effects were detected in the animals with 50 ppm of lindane (in a 10% corn-oil solution) in their diet. At 100 ppm, the rats developed slightly enlarged livers; microscopic examination of liver and kidney tissue revealed damage described as "very slight." At 800 and 1600 ppm, nervous symptoms and convulsions developed and a few rats died.[59]

For a period of 3 mo, Desi fed rats daily lindane doses of 1/40 and 1/20 of the LD_{50}.[99] The LD_{50} was determined to be 100 mg/kg of body weight; thus, the administered doses were 2.5 and 5.0 mg/kg of body weight. The rats were evaluated for EEG abnormalities and learning deficiencies, in addition to standard toxicological evaluations of weight gain, blood analysis, and histopathological examination. At the lower dose, no alteration in EEG pattern was exhibited, nor was there any effect on the rats' ability to learn a maze. At the higher dose, however, altered EEG patterns

Table 7. No-observable-effects levels reported from various animal studies.

Daily dose (mg/kg body wt)	Daily dose (ppm in feed)	Species	Duration of study	Ref.
1.25[a]	25	Rat	2 y	109
2.50[a]	50	Rat	Lifetime	59
2.50	50[a]	Rat	3 mo	99
1.6[b]	50	Beagle	2 y	47

[a] Estimated by considering a ratio of ppm in feed to mg/kg of body weight of 20 to 1 to be reasonable for the adult rat.[43]

[b] Mean daily-dose equivalent reported after 104 wk, based on food consumption and body weight.[47]

developed. The rats consuming the higher dose of lindane made substantially more mistakes in the maze-running trials until about the 30th day of the experiment, when the number of mistakes suddenly dropped to the same level as that of the controls and lower-dose group. The authors offered no explanation for the sudden drop in the number of mistakes.

Carcinogenicity

The International Agency for Research on Cancer (IARC) reviewed the literature on the carcinogenicity of technical-grade HCH and individual HCH isomers.[111] The working group concluded that sufficient evidence exists that alpha-HCH, lindane, and technical-grade HCH are carcinogenic in mice (i.e., producing liver tumors when administered in the diet). The IARC review also concluded that human epidemiological data were not adequate to support a similar conclusion for humans. The reviewers noted that many chemicals exist for which there is sufficient evidence of carcinogenicity in animals, but for which the human data are either insufficient or nonexistent. In these cases, they believe "it is reasonable, for practical purposes, to regard such chemicals as if they presented a carcinogenic risk to humans."[111]

DEVELOPMENT OF RECOMMENDATIONS FOR STANDARDS

Major uncertainties exist in the method for calculating the standard and in the data on which the calculations are based. In addition, assumptions were required to bridge gaps in the current knowledge about the health effects of HCH and lindane.

METHOD AND RATIONALE

The 1-y recommended standard is based on an evaluation of the daily dose of lindane that produced no adverse effects in rats in one lifetime feeding study and slight liver enlargement in another,[59,109] and the lowest daily dose reported to cause adverse effects in humans.[80] A safety factor of 10 is applied to the lowest daily dose reported to cause adverse effects in humans (30 mg/d)[80] to arrive at an acceptable daily dose for humans who will be exposed for up to 1 y. The acceptable daily dose is divided by the assumed daily water consumption to arrive at the recommended standards. The recommended 7-d standard is the same as the 1-y recommendation.

No-Performance-Degradation Dose (1 y)

The acceptable daily intake proposed by WHO is based on a NOEL in rats calculated to be 1.25 mg of lindane in feed/kg body weight per day.[110] When 2.5 mg lindane was ingested/kg body weight per day (estimated from 50 mg/kg diet), liver enlargement occurred.[109] Fitzhugh et al. also conducted a long-term feeding study in rats and found no observable effects at 50 mg lindane/kg diet.[59] In another feeding study involving a diet containing lindane at a concentration of 100 mg/kg of feed, they observed slight liver enlargement, and microscopic examination of the liver and kidney revealed damage described as "very slight."

The WHO applied a 100-fold safety factor to the no-effects level found in rats (i.e., 1.25 mg/kg body weight/d) to arrive at their recommended acceptable daily intake (ADI) of 0.01 mg/kg for humans.[110] The 100-fold safety factor is commonly applied when extrapolating data concerning chronic health effects from animals to humans. The ADI, however, is an intake level judged to be acceptable for a lifetime exposure. Because the purpose here is to develop an acceptable intake for a 1-y exposure, we consider it appropriate to base the acceptable intake on the minimal-effects level found in animal studies, rather than on the no-effects level, and to use a smaller safety factor.

Using the procedure just described, the dose that would be acceptable for a 1-y human exposure is calculated by applying a safety factor of 10 to a "minimal-effects"

dose from animal studies (2.5 mg/(kg • d)). The use of a minimal-effects level rather than a no-effects level is thought to be reasonable and conservative because the animal study that indicated this daily-dose rate could cause liver hypertrophy was a lifetime feeding study, and the standard is to protect against adverse health effects from exposures of up to 1 y. The safety factor is applied to account for uncertainties of extrapolating from animals to humans. Another safety factor of 10 is often applied to extrapolations of this sort to account for differences in sensitivity among the human population. This amounts to a total safety factor of 100, such as that applied by the WHO in derivation of the ADI. However, a working assumption of the field-water criteria documents is that military populations do not include the subpopulations generally considered to be the most sensitive to adverse health effects of pollutants (i.e., infants, the elderly, the infirm). Thus, we do not believe that it is necessary to apply an additional safety factor.

By applying a 10-fold safety factor to a minimal-effects-level dose of 2.5 mg/(kg • d), the estimated tolerable dose for 1 y would be 0.25 mg/(kg • d). At this rate, the daily intake for a 70-kg adult would be 17.5 mg/d. This daily dose is only 58% of that which caused acute toxicity in humans (i.e., 30 mg/d).[80] The fact that the lowest daily dose that caused adverse effects in humans (30 mg/d) is so close to the daily dose that would otherwise be considered safe (17.5 mg/d), based on extrapolation from an animal lifetime feeding study, suggests that humans may be more sensitive to lindane than laboratory animals (i.e., rats). Accordingly, a further reduction in the maximum allowable daily dose is judged necessary. Therefore, we recommend that a dose of 3 mg/d be used as the maximum allowable daily dose of lindane. This daily dose is a factor of 10 lower than the lowest one reported to cause adverse effects in humans.

The calculation of the 1-y standard, using daily water-consumption rates of 5 and 15 L, are shown below.

$$\frac{3\ \text{mg/d}}{5\ \text{L/d}} = 0.6\ \text{mg/L}; \qquad \frac{3\ \text{mg/d}}{15\ \text{L/d}} = 0.2\ \text{mg/L}.$$

If troops are exposed to technical-grade HCH (i.e., mixed isomers) rather than pure lindane, a standard based on pure lindane may not protect troops against the chronic toxicity of the alpha- and beta-isomers. When rats were given feed containing 10 mg of technical-grade HCH/kg in a lifetime feeding study, no adverse effects were found.[59] At 50 mg of technical-grade HCH/kg in their diet, the effect noted was "very slight" liver damage, which was noted in microscopic examination of liver tissue. As mentioned above, the same authors observed no effects in rats fed 50 mg of lindane/kg in their diet. At 100 mg of technical-grade HCH/kg in the diet, the observed effects included a slight increase in liver weight and microscopic damage described as "slight." No damage to the

kidneys was found, but a slight brown pigmentation of the convoluted tubular epithelium was evident.[59] It thus appears that technical-grade HCH is somewhat more toxic than lindane alone in chronic exposure situations.

It should also be noted that the composition of mixed-HCH isomers in water may be different from the composition of technical-grade HCH as described in Table 1. This is because of differences in the water solubility of the various isomers. Thus, technical-grade HCH in water may become relatively depleted of the less water-soluble beta-isomer. With a depletion in water of the most toxic isomer, from the perspective of chronic exposures, i.e., beta, it would be reasonable to expect that results from long-term animal feeding studies would differ depending on whether technical-grade HCH or the beta-isomer was used.

To protect against the health effects of HCH, it may also be necessary to set separate standards for the other major HCH isomers, alpha and beta. For further consideration, such standards can be derived by applying a 10- to 100-fold safety factor to the minimal effects levels reported for these two HCH isomers in lifetime feeding studies of laboratory rats.[59] The selection of an appropriate safety factor is judgmental and based on consideration of the amount of uncertainty associated with the extrapolation of animal doses to equivalent human doses. Large safety factors add conservatism to a standard and account for greater degrees of uncertainty. Based on data from the lifetime feeding studies, the minimal effects level in rats for the alpha-isomer is considered to be a daily dose of 2.5 mg/kg of body weight (estimated from an administered daily dose of 50 mg/kg feed), and the corresponding level in rats for the beta isomer is considered to be a daily dose of 0.5 mg/kg body weight (estimated from an administered daily dose of 10 mg/kg feed). Accordingly, the following equation can be used to calculate proposed field-water-quality standards for these two HCH isomers for 70-kg military personnel, an exposure period of up to 1 y, and consumption rates of 5 or 15 L/d.

$$C = \frac{D \times W}{SF \times Q} \qquad (1)$$

where

- C = proposed field-water-quality standard (mg/L);
- D = daily dose rate estimated from minimal effects level in lifetime feeding studies of laboratory rats (mg/(kg•d));
- W = standard weight of military personnel (kg);
- SF = 10- to 100-fold safety factor (dimensionless); and
- Q = drinking-water consumption rate (L/d).

Thus, possible standards for alpha-HCH are 3.5 and 1.2 mg/L for a 10-fold safety factor and 5 and 15 L/d consumption rates, or 0.35 and 0.12 mg/L for a 100-fold safety factor and similar water-consumption rates. For beta-HCH, possibe standards are 0.7 and 0.23 mg/L for a 10-fold safety factor and 5 and 15 L/d consumption rates, or 0.07 and 0.023 for a 100-fold safety factor and similar water-consumption rates. However, in a literature search for reports of pesticide levels in water, we found only one reported concentration of alpha-HCH and of beta-HCH (i.e., 0.83 mg/L; see Vol. 2, Part 2 of this report) that might be of possible concern. The reason for such possible concern is because the reported concentration is in excess of the lower limits of the standards recommended for consideration for alpha-HCH and in excess of both the upper and lower limits of the standards recommended for consideration for beta-HCH. Because the literature contains only one reported concentration of alpha- and beta-HCH isomers of possible concern, further research is needed to determine if additional standards for the HCH isomers other than gamma are essential for the military.

No-Performance-Degradation Dose (7 d)

The short-term dose regimens for lindane that produced no adverse reaction in humans included: (1) 45 mg/d in a lipid carrier for 3 d[80]; (2) 90 mg/d in a lipoid carrier, apparently for 3 d[80]; (3) 40 mg/d as a solid for 14 d[79]; and (4) 100 mg/d as a solid for 14 d.[79] In contrast to these, a single dose of 45 mg caused convulsions in one patient, and 30 mg/d for 3 d caused nausea, stomach pains, and diarrhea in three patients, as well as dizziness and vision problems in a fourth patient. Thus, there appears to be no dose reported in the literature that could be considered a no-adverse-effects dose in humans. Therefore, it is recommended that the 7-d standard be established at the same level as the 1-y standard, which is based on observations in human studies.

MAJOR UNCERTAINTIES AND ASSUMPTIONS

The most important uncertainties are associated with the derivation of the no-effects doses for lindane that serve as the bases for our recommended standards. No studies of long- or short-term human exposure characterized the doses sufficiently to allow the identification of a no-effects level. Consequently, the recommended standards are based on an evaluation of animal studies and available human data, and the resulting incorporation of a safety factor with the lowest dose reported to cause adverse effects in humans. The use of the lowest dose reported to cause adverse effects in humans and the application of a 10-fold safety factor are judged to provide a standard that adequately

protects troops who will be exposed to lindane in field water for up to 1 y. With regardto the 7-d standard, an important uncertainty is the apparent high degree of individual variability in sensitivity to lindane. Furthermore, human clinical trials suggest that exposure to mixed-HCH isomers may cause symptoms such as headache and nausea at doses below those that cause lindane toxicity.[79] Thus, recommendations for the alpha- and beta-isomer exposure limits are also included in this report.

At low exposure levels, lindane can cause changes in the nervous system that can be detected in EEG recordings, by behavioral tests, and in some cases, by clinical neurological examination. Observations of extinction and attenuation of effects after termination of lindane exposure suggest that lindane-induced adverse health effects may be reversible. Furthermore, the mild symptoms reported (i.e., nonspecific EEG changes) are judged not to be performance-degrading. However, conclusions about reversibility and effects on human performance are somewhat uncertain because the significance of some of the results and the biochemical nature of the subtle nervous system changes are not known precisely. Having stated these caveats and based on the data available to date and presented in this document, we assume that the mild nervous system changes detected by the previously mentioned techniques are neither performance-degrading nor irreversible with regard to exposed military personnel.

RECOMMENDATIONS FOR STANDARDS

The lindane drinking-water standards that we recommend for military field water and limited duration of exposure (5- and 15-L/d consumption rates for periods up to 7 d and 1 y) are shown in Table 8. As evident in the table, the recommended standards are much higher than the standards promulgated by the U.S. EPA for lindane. The EPA standards assume a lifetime exposure period, and they assume that lindane is a carcinogen.[112] The ADI recommended by the WHO/FAO is also based on a lifetime exposure period.[110] The occupational standard for inhalation of lindane is 0.5 mg/m^3.[113,114] The occupational standard is computed from time-weighted averages and assumes an exposure of 8 h/d during a 5-d work week. The occupational exposure standard is also based on health effects other than cancer.[113,114] The occupational standard for concentrations of lindane in the air was converted to a drinking-water standard by the method of Stokinger and Woodward.[115] These assumptions were made for the calculations: (1) lindane is completely absorbed by both inhalation and ingestion, and (2) a worker will inhale 10 m^3 of air per 8-h day.

The recommended standards for lindane are based on an allowable daily dose of 3 mg/d. The occupational standard converts to an allowable daily dose for lindane of

Table 8. Comparison of recommended drinking-water standards for lindane.

Recommended standard (mg/L)		Assumed water consumption	
≤ 7 d	≤ 1 y	(L/d)	Source
0.6	0.6	5	Maximum concentration recommended by this study.
0.2	0.2	15	Maximum concentration recommended by this study.
	0.004[a]	2	U.S. EPA, 1980.[112]
	0.14[a]	5	Concentration equivalent to WHO/FAO ADI.[110]
	0.05[a]	15	Concentration equivalent to WHO/FAO ADI.[110]
	1.0	5	Concentration equivalent to occupational standard of 0.5 mg/m^3.[113]
	0.3	15	Concentration equivalent to occupational standard of 0.5 mg/m^3.[113]

[a] Lifetime exposure assumed for this standard.

about 5 mg/d (see Table 9). Although the recommended standards are slightly lower than the one estimated from the occupational standard for lindane in air, we consider them to be justified on the basis of applying a 10-fold safety factor to the lowest daily dose of lindane that could cause acute toxicity, based on evidence from human experiments.[80]

Because technical-grade HCH may be more toxic than lindane alone for some chronic exposure situations, we calculated ranges of concentrations limits for the major isomers of HCH other than the gamma isomer (i.e., the alpha- and beta-isomers). However, a review of reported pesticide levels in water worldwide revealed only one instance where the concentration of these isomers ever exceeded any of the limits recommended for consideration as standards. Therefore, further research is needed to determine if standards for isomers of technical-grade HCH are really necessary.

Table 9. Comparison of daily doses for lindane.

Daily dose (mg/d)	Source and description
30	Caused vision problems, dizziness, and gastrointestinal problems in humans.[79]
6	Dose corresponding to OSHA standard.[113]
3	Dose corresponding to standard recommended by this study.
0.7[a]	Dose corresponding to ADI.[110]
0.008[b]	Dose corresponding to EPA drinking-water standard.[112]

[a] 0.01 mg/(kg•d) x 70 kg.

[b] 0.004 mg/L x 2 L/d.

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CHAPTER 10. ALGAE AND ASSOCIATED AQUATIC BACTERIA

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ABSTRACT

Algae and associated aquatic microorganisms are commonly found in fresh and marine waters. Many of these microorganisms have been identified as the source of taste and odor (organoleptic) problems in surface waters, particularly drinking-water reservoirs. Two of these microorganisms, cyanobacteria (blue-green algae) and actinomycetes (gram-positive filamentous bacteria that grow in close association with cyanobacteria), are important from the perspective of military field-water quality because they can release the compounds geosmin and 2-methylisoborneol (MIB), into water. These substances are persistent and can cause taste and odor problems at extremely low concentrations. Furthermore, cyanobacteria are the source of other biochemicals (i.e., alkaloid, lipopolysaccharide, and polypeptide compounds) that are considered to be toxic to animals and therefore to man. In this chapter we discuss the potential impact field water containing these biochemicals can have on the performance of military personnel if they consume such water. Field-water-quality standards are recommended for the taste- and odor-causing biochemicals, geosmin and MIB, because data are sufficient to support such recommendations.

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INTRODUCTION

Algae and associated aquatic microorganisms are commonly found in fresh and marine waters. Many of these aquatic microorganisms have been identified as the source of taste and odor (organoleptic) problems, particularly in drinking-water reservoirs.[1-3] Cyanobacteria (blue-green algae) and actinomycetes (gram-positive filamentous bacteria that grow in close association with cyanobacteria) are the most important of these microorganisms from a military field-water-quality perspective because they can release the compounds geosmin and 2-methylisoborneol (MIB), into water.[2,4-9] These substances are persistent and can cause taste and odor problems at extremely low concentrations. For example, detection thresholds for the taste and odor of geosmin and MIB are under 10 ng/L.[2,10,11] Accordingly, military personnel might refuse to drink field water containing such compounds and thereby may become susceptible to dehydration and its performance-degrading health effects. The health implications of refusing to drink field water on the basis of its organoleptic properties are greatest for military populations in hot, arid environments where large amounts of water are needed to replace sweat losses.

Fresh-water cyanobacteria may also produce other biochemicals (i.e., alkaloid, lipopolysaccharide (LPS), and polypeptide compounds) that might be of military concern. For example, poisonings of livestock and domestic animals have been attributed to ingestion of water containing these substances and/or concentrated masses of the cells that produce them.[12-14] Moreover, there is circumstantial evidence that indicates that a causal relationship exists between otherwise unexplainable outbreaks of adverse health effects in human populations and the presence of cyanobacteria and their toxic biochemicals in public drinking-water supplies.[15-22]

Typically, cyanobacteria and actinomycetes will be encountered by military personnel in surface waters, especially reservoir-type bodies of fresh water; however, marine forms also exist.[23,24] Accordingly, should these marine microorganisms produce organoleptic or toxic substances that can pass through a reverse osmosis water purification unit (ROWPU), which U.S. military forces will employ to make sea water potable, then such water might be unacceptable for consumption without additional treatment.

Virtually all the reported incidents of animal or human poisoning and most of the accounts of organoleptic problems just mentioned correlate with the presence of heavy blooms of cyanobacteria and actinomycetes (an algal bloom is the accumulation of

dense masses of algae and accompanying bacteria along shore lines as a consequence of wind and wave action) in drinking water. Usually, blooms occur as part of the eutrophication process (i.e., the increase in biological productivity of a water body and subsequently, its detritus content, as a result of favorable temperature and nutrient enrichment introduced naturally or as a consequence of pollution from human activities) in surface waters. Thus, the biochemicals of military concern are most likely to be at critical levels only when algal blooms are present.

The general properties, methods of detection, and potential direct and indirect health consequences associated with the presence of these microorganisms and their biochemicals in potential sources of field drinking-water supplies are reviewed next. Based on these data we develop recommendations for standards, or pragmatic alternatives to such standards, that are applicable to military populations consuming up to 5 and 15 L/d of water for periods up to 7 d and 1 y.

GENERAL PROPERTIES OF CYANOBACTERIA AND ACTINOMYCETES

All algae and bacteria are members of the kingdom Protista. Protists are distinguished from plants and animals primarily by their simple cellular organization. The algal protists are divided into two categories: (1) blue-green algae, commonly referred to as cyanobacteria, and (2) all other forms of algae, which include the brown, green, and red algae, as well as the dinoflagellates. Cyanobacteria, as well as typical bacteria like actinomycetes, are considered lower protists because they are prokaryotic cells (i.e., a nuclear membrane is absent). All other algae are higher protists because they are eukaryotic cells (i.e., genetic material is surrounded by a nuclear membrane).

In natural waters, especially fresh surface waters, cyanobacteria grow in close association with the bacteria actinomycetes; the cyanobacteria are postulated to be a source of nutrition for the actinomycetes, which peak in population once the cyanobacteria population starts its decline.[4] As mentioned earlier, marine forms of these algae and bacteria also exist and may exhibit a similar relationship.[23,24]

BIOCHEMICALS RELEASED BY CYANOBACTERIA AND ACTINOMYCETES AND THEIR OCCURRENCE

Both cyanobacteria and actinomycetes release biochemicals that can impair the taste and odor of water at very low concentrations.[2,4-9] These substances are

geosmin and 2-methylisoborneol (MIB). Both geosmin and MIB are persistent and can cause earthy/musty organoleptic problems at extremely low concentrations. For example, detection thresholds for the taste and odor of geosmin and MIB vary from 1 to 10 ng/L, depending on the sensitivity of the individual.[2,10,11] Furthermore, some cyanobacteria also produce alkaloid, lipopolysaccharide, and polypeptide compounds that can be released into water. These biochemicals might also be of military concern because they have been implicated as being toxic to humans.[15-22]

Organoleptic Metabolites: Geosmin and MIB. Geosmin (trans-1, 10-dimethyl-trans-9-decalol) and MIB (2-methylisoborneol) are cyclic, tertiary alcohols that have been isolated from both algae and actinomycetes.[7,8,25] These substances are not easily removed by chlorination at the low concentrations at which they are a nuisance in drinking-water supplies.[26]

The occurrence of earthy-musty taste and odor in water supplies appears to be a world-wide problem. For instance, accounts of taste and odor problems due to geosmin and MIB contamination in drinking water supplies have been reported in Canada, The Netherlands, Japan, and Israel.[11,27] Persson[11] also mentions the occurrence of cyanobacteria/actinomycetes-associated taste and odor problems in drinking waters in Argentina, Australia, Austria, Czechoslovakia, Denmark, Finland, Germany, Norway, Poland, Sweden, the United Kingdom, and the Soviet Union. Piet et al.[28] report the presence of geosmin and MIB in river, lake, and North Sea water of The Netherlands. Yagi et al.[29] state that in August 1981 a maximum geosmin concentration of 400 ng/L was confirmed in the largest lake in Japan, Lake Biwa. In this lake in June 1982 MIB reached a maximum concentration of 130 ng/L. Hwang et al.[30] indicate that selected samples of water collected from aqueducts, and terminal reservoirs serving California contained geosmin and MIB concentrations ranging between 2 and 36 ng/L.

Toxic Biochemicals: Alkaloid, Lipopolysaccharide, and Polypeptide Compounds. Alkaloid, lipopolysaccharide (endotoxins), and polypeptide biochemicals produced by certain cyanobacteria have been implicated as the etiologic agent of fatal toxicity in cattle[12] and domestic animals.[14] Circumstantial evidence suggests that these substances also may be toxic to humans.[15-22] The polypeptide and lipopolysaccharide toxins are found in close association with the cell wall of the organism[12,20] and are probably released into the water after the cell dies and degradation of the cell wall takes piace.[17,18,31] The alkaloid toxins apparently are released directly into water by the living organisms.[32] All three categories of potentially toxic compounds appear to be water soluble.

Incidents of human health effects reported to result from either ingestion or nonconsumptive exposure to aquatic blooms of cyanobacteria are summarized in Table 1.

Until very recently only one alkaloid toxin, anatoxin-a, had been defined chemically, toxicologically, and pharmacologically.[35] Anatoxin-a has a molecular weight of 165 daltons[36] and has the chemical name 2-acetyl-9-azabicyclo[4.2.1]non-2-ene.[35] The structure of anatoxin-a is similar to cocaine but this biochemical does not possess the same pharmacological properties. However, the spatial arrangement of the molecule is similar to acetylcholine[32] and anatoxin-a is a powerful neuromuscular blocking agent.[35] Furthermore, laboratory rodents injected with lethal doses of anatoxin-a exhibit ataxia and convulsions prior to death.[32] The more recently discovered anatoxin differs in its pharmacological properties and signs of poisoning from anatoxin-a, but it has been named anatoxin-a(s) because of gross toxicological similarity to anatoxin-a. However, anatoxin-a(s) causes salivation (s) and anatoxin-a does not.[35] Anatoxin-a has generally been the alkaloid toxin identified in waters of potential concern from a public health perspective.

According to Keleti et al.[22] lipopolysaccharides are constituents of the outer cell wall of cyanobacteria. Additionally, the LPS component of the cell wall consists of three regions; an O-specific polysaccharide with repeating oligosaccharide units that are responsible for antigenic specificity, a basal-core oligosaccharide, and a hydrophobic lipid called lipid A.

A simple analytical method for measuring the concentration of lipopolysaccharide (LPS) compounds in water is available. The measurement is made using a Limulus amoebocyte lysate (LAL) test. Table 2 shows concentrations of LPS measured in waters in the United States. According to Gerba[37] the ground waters reported in Table 2 were located under wastewater lagoons, and it is conceivable that the LPS entered the aquifer after the organisms had degraded on the bottom sediment of the lagoon. However, the process of groundwater contamination by algal endotoxins like LPS has not been well defined. Alternatively, an LPS concentration of 2.5 mg/L was recorded in a drinking water system in Pennsylvania at the time of an algal bloom and coincident with an outbreak of gastroenteritis of unknown origin. Normal levels of LPS in the reservoir were between 0.025 and 0.25 mg/L.[22]

The peptide toxins are not well characterized chemically or toxicologically.[13,38] The toxicity of these molecules is probably related to their unusual chemical attributes such as rare amino acids and cyclic configurations.[38]

Table 1. Summary of locations where adverse human health effects were attributed to the occurrence of blooms of toxin-producing cyanobacteria.

Water	Location	Refs.
Sea Water	Okinawa Island, Japan	21
Fresh Water	Dacca, Bangladesh	15
Fresh Water	Sewickley, Pennsylvania, USA	22
Fresh Water	Clark Air Force Base, Philippines	19
Fresh Water	South Africa	33
Fresh Water	Europe	31
Fresh Water	Northeast Pennsylvania, USA	16
Sea Water	Oahu, Kahala Beach, HI, USA	34
Fresh Water	Armidale, Australia	18

Table 2. Lipopolysaccharide (LPS) concentrations measured in tapwater and groundwater using a Limulus amoebocyte lysate test.[37]

Water	Concentration (ng/L)	Location
Tap water	0.3	Ft. Devens, MA, USA
Ground water	0.6 to 30	Ft. Devens, MA, USA
Ground water	120 to 480	Lubbock, TX, USA
Ground water	3	Phoenix, AZ, USA

Although eurkaryotic algae, especially the green and yellow-green varieties and the dinoflagellates, also produce metabolites that have been reported to cause adverse health effects in humans,[36,38] these organisms and their metabolites are not of concern from the perspective of military field-water quality. This is because the toxic effects attributed to them are typically the result of the bioaccumulation of the compounds in aquatic organisms consumed by man. For example, the marine dinoflagellate Gonyalux catenella, releases a toxic metabolite that can accumulate in shellfish and then be passed on to man following ingestion of the organism; the result is paralytic shell-fish poisoning.[38]

ANALYTICAL METHODS

Analytical methods are still evolving for routinely determining the concentration in water of the alkaloid and peptide toxins released by cyanobacteria. High-pressure liquid chromatography (HPLC) in combination with ultraviolet spectrophotometric measurement has been developed for isolating and quantifying aqueous solutions of anatoxin-a.[32,39] This assay reportedly can detect as little as 0.1 mg/L of anatoxin-a,[32] but is more suited to the laboratory than a field environment.

Extremely low concentrations of geosmin and MIB can be detected using a closed loop stripping technique in combination with a gas chromatograph/mass spectrometer (GC/MS).[26,40,41] The detection limit for this technique has been reported to be as low as 0.8 ng/L for both geosmin and 2-methylisoborneol.[30] The benefit of closed loop stripping is that it can concentrate semivolatile organic compounds from water by means of a recirculating stream of air. Activated carbon is used to remove the organic chemicals from the gas phase. The organic compounds are then extracted from the carbon filter for analysis with a GC/MS. However, this analytical procedure cannot be considered suitable for field application.

As mentioned earlier, concentrations of LPS (endotoxin) can be detected in natural waters by the Limulus amoebocyte lysate (LAL) test.[20,22,42,43] Basically, this technique involves mixing an extremely small quantity of a water sample with an equal amount of a lysate prepared from the amebocytes of the horseshoe crab, Limulus, and incubating the resulting mixture for about one hour, undisturbed, at a temperature of 37°C. The formation of an opaque gel or turbidity indicates the presence of LPS in the water. The test is made semiquantitative by serially diluting the test solution and determining the gelation endpoint of each dilution. The LAL test can easily detect as little as 1 ng/mL (ppb) of LPS.[42,43]

Although, non-specific reactions of organic compounds other than LPS may affect the results,[22] the LAL test can be a useful tool for field work because it can be used to confirm the presence of algae and its byproducts, including LPS, in as little as one hour. Because incubation at 37°C is an essential step in the LAL test for detecting LPS in water, an incubator will be required in the field.

HEALTH EFFECTS

The two different types of performance-degrading health effects that might result from the presence of high concentrations of cyanobacteria and actinomycetes in a field water are (1) indirect effects related to the release of the organoleptic metabolites geosmin and MIB by both cyanobacteria and actinomycetes, and (2) direct effects associated with the toxicity of alkaloid, LPS, and polypeptide compounds that may be released by cyanobacteria. The indirect effects occur because many military personnel will reduce their consumption of water with an objectionable taste and odor, and in many operating regions, especially desert areas where large amounts of water are needed to replace sweat losses, this action could lead to dehydration and the performance degrading effects associated with it. Both indirect and direct effects are most likely to occur only as a consequence of algal blooms.

Geosmin and MIB are produced by a wide variety of cyanobacteria and actinomycetes,[2-9,24-26] whereas the alkaloid, LPS, and polypeptide toxins generally are attributed to only a few species of cyanobacteria, Microcystis aeruginosa, Anabaena flos-aquae, and Schizothrrix calcicola.[12-14,22,36,38] No actue or chronic adverse health effects are known to be associated with oral ingestion of the extremely low concentrations of geosmin and MIB that produce taste and odor problems. However, as we mentioned in an earlier section, deaths of cattle and domestic animals have been attributed to consumption of water containing alkaloid, LPS, and polypeptide toxins[12,14] and circumstantial evidence from laboratory epidemiological studies suggests that these substances may also be responsible for toxic effects in humans.[13-22] The toxicity of alkaloid, LPS, and polypeptide toxins with respect to humans is summarized next.

Until recently, the most chemically and pharmacologically understood alkaloid toxin has been anatoxin-a.[13,35] However, no human deaths have been directly correlated with the ingestion of water containing alkaloid toxins. Lipopolysaccharides (endotoxins) have been isolated from common gram-negative

bacteria and cyanobacteria.[20,22] Characteristic responses by humans to LPS from gram-negative bacteria are endotoxemia (the presence of endotoxin in the blood) and pyrogenicity (fever).[20] However, the effect on human populations of ingestion of drinking water containing LPS of cyanobacterial origin is a controversial subject because there is little evidence to suggest that a normal population would be affected by ingesting drinking water containing LPS.[13] Nevertheless, gastroenteritis and "travellers' diarrhea" have been attributed to elevated concentrations of LPS in drinking water supplies in Mexico City (0.8 mg/L) and Sewickley, PA (2.5 mg/L or 10 to 100 times normal conditions).[20,22] Information about the polypeptide toxins is limited. However, evidence presented by Falconer et al.[44] indicates that a bloom of Microcystis aeruginosa in a reservoir containing drinking water for the city of Armidale, Australia, was probably responsible for an increased incidence of liver damage among members of the population using that water. According to Falconer et al.[44] the pentapeptide hepatotoxin of Microcystis aeruginosa enters water when the cells are damaged. Consequently, the toxin may be released in the stomach or rumen of livestock following ingestion of drinking water containing the alga or it may be present in the water following lysis of the cells in the course of treatment of the water with an algicide or after travel through a distribution system.

RECOMMENDATIONS FOR STANDARDS

Unfortunately, data are too limited for recommending standards for the toxic substances associated with the presence of cyanobacteria in algal blooms. Although the toxic agents have been shown to produce toxicity in livestock, domestic and laboratory animals; interspecies extrapolation is made difficult by too many confounding variables (e.g., differences in digestive systems, responses, and dosage equivalents). The practical recommendation is that field waters containing algal blooms be avoided by military personnel or be used only after treatment with activated carbon, because such waters may contain natural biological substances that can produce performance-degrading health effects in military populations.

Alternatively, field-water-quality standards of 10 ng/L are recommended for both geosmin and MIB. Although there is no evidence that these substances are toxic, especially at an extremely low concentration; at higher concentrations they may indicate the presence of other potentially toxic biochemicals, especially if algal blooms are apparent. Because the recommended standards are based on the

organoleptic properties (i.e., taste and odor) of these algal metabolites, they are applicable to both short- ($\leq$ 7-d) and long-term ($\leq$ 1-y) periods of exposure, as well as to any consumption rate, including 5 and 15 L/d.

Development of Standards for Geosmin and MIB

The recommended standards for geosmin and MIB were adjusted for military populations from data presented in the literature regarding the response of individuals to drinking water containing objectionable taste or odor. These data are described next.

First, Zoeteman and Piet[45] reported that people who disliked tapwater on the basis of its taste consumed 45% less than those individuals drinking tapwater that they liked. Accordingly, military personnel might also reduce or refuse consumption of water possessing objectionable taste and odor and thereby become susceptible to the adverse effects of dehydration.

In another study performed for the U.S. Environmental Protection Agency, Lillard and Powers[46] used a statistical method to estimate the percentage of the general population that might have odor thresholds for geosmin and other organic pollutants in aqueous solution that are lower than those exhibited by a panel of judges. The results of this research show that at the 95% confidence level less than 20% of the population might still be able to detect geosmin at concentrations lower than 10 ng/L. Similarly, only about 10% of the general population might detect geosmin at concentrations less than approximately 4 ng/L. Unfortunately, MIB was not used in this study and so we assume similar sensitivities apply to the general population for that compound in aqueous solution.

Finally, Burlingame et al.[3] examined the relationship between geosmin concentration in the source and treated water supplying 20% of the water used in Philadelphia, and the consumer acceptance of the water. The geosmin was associated with an algal bloom in the source water. Their analysis revealed that customer complaints were many when the geosmin concentration exceeded 45 ng/L, but were minimal when the level was less than 30 ng/L. Background levels for geosmin were determined to range from 10 to 20 ng/L. On the basis of the data concerning customer complaints, a target level for geosmin of 30 ng/L was established. This target level was established with the understanding that customers will respond to changes in taste and odor, to the intensity of a taste and odor, and to the persistence of a taste and odor. It was also known that both

geosmin and MIB can cause sensory fatigue, rapidly dulling the sensitivity of an individual to these earthy/must odors.[3,28] Interestingly, Means and McGuire[2] note that consumer complaints are received by the Metropolitan Water District of Southern California when the concentration of MIB in water leaving treatment facilities exceeds 8 to 10 mg/L.

Because of the importance of water for military personnel, particularly in hot, arid environments, we recommend that levels for geosmin and MIB not exceed 10 ng/L. This concentration is considered safe and tolerable, especially for military personnel consuming large volumes of water, for the reasons following. First, water containing levels of geosmin or MIB at concentrations less than or equal to 10 ng/L is not likely to contain algal toxins, because it is unlikely to contain an algal bloom. Furthermore, this concentration should not cause sensory fatigue, which could lead to consumption of water that contains algal toxins. Moreover, 10 ng/L was the level detected upstream from the floating masses of algae that were determined to be the source of geosmin concentrations that exceeded 30 ng/L and precipitated consumer complaints in Philadelphia.[3] It is also the concentration above which consumer complaints are received by the Metropolitan Water District of Southern California.[2] Consequently, this concentration should not only protect military personnel from ingesting algal toxins with drinking water but also produce the fewest complaints and least amount of rejection among military personnel thereby minimizing the potential risk of performance degradation from dehydration. As pointed out by Bourke et. al.[17] the human dislike for discolored, foul-tasting, malodorous water is probably the reason for minimal information concerning human algal intoxication.

We conclude by noting that the taste- and odor-producing metabolites of algae might be increased by lysis of the cells and therefore it is best not to use an algicide to eliminate the algal mass in hopes of immediately obtaining drinking water. Furthermore, the chemical nature of these odors makes them difficult to remove by standard methods of chlorination.[40] Consequently, waters that have obvious algal masses and detectable earthy/musty odors should be avoided.

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CHAPTER 11. RESEARCH RECOMMENDATIONS

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ABSTRACT

The field-water-quality standards recommended for adoption by the Armed Forces of the United States were developed in the face of limited and sometimes discordant data. Research necessary to reduce important sources of uncertainty or to strengthen the scientific basis of the recommended standards is described. This research should include human studies with military personnel under field conditions so that the relationship between the organoleptic properties of water and the desire to consume such water is made more clear. Also, toxicological and pharmacological studies employing suitable animal models should be performed to explain the mechanisms of action of the more toxic substances such as arsenic, and cyanide. Finally, future research should examine the synergistic effects that combinations of constituents in field water can have on military performance. Among the most important research studies recommended are those addressing (1) the complex relationship between temperature, pH and odor, and the influence these factors can have on fluid consumption, especially in a hot, arid environment, (2) the relationship between turbidity and disinfection, (3) the effects of magnesium and sulfate with respect to the organoleptic and laxative properties of total dissolved solids, (4) the precise implications of chloride concentration as it relates to salt ingestion that is added to that obtained from military rations and with respect to operation of reverse osmosis water purification units, (5) the nature of the human health effects associated with different chemical species of arsenic, (6) the importance of excretion pathways, such as sweating, with regard to cyanide detoxification and elimination, (7) the dose-response relationship for lindane with regard to subtle neurological changes and military performance, and (8) the consequences of ingesting water containing concentrations of toxins released by cyanobacteria.

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INTRODUCTION

During the course of our work on the field-water standards dealing with water properties and chemical constituents of concern, we encountered various kinds of uncertainties and data gaps that affected our ability to develop standards for managing the potential health risks of field waters used as sources of drinking water. The goal of this chapter, therefore, is to recommend research that can provide results that may be directly used to improve the standards. Specifically, we address research that will help reduce important sources of uncertainty or strengthen the scientific basis of the standards. The research recommendations are presented for temperature, pH, and odor, and for each water-quality parameter of concern.

TEMPERATURE, pH, AND ODOR

The complex relationship between temperature, pH, and odor in field water and the influence of these factors on fluid consumption is not well defined. Available data only describe generalized tolerable limits for these properties consistent with palatable, potable water. In fact, a potential source of drinking water may not be consumed if the temperature, pH, and/or odor of the water were outside the tolerable limits, independent of the concentration of any other chemicals or properties of concern present in the water. For example, research reported by Hubbard et al.[1] shows that volunteer military personnel subjected to a 6-h, 9-mile simulated desert walk and given water that was flavored and at the optimum preferred temperature of 15°C (59°F) significantly increased their amount of voluntary rehydration (consumption increased a maximum of 120%) over those volunteers subjected to similar conditions but given warm iodine-treated water at a temperature of 40°C (104°F). Moreover, volunteers were reluctant to consume the warm halogen-treated water and these individuals suffered significant hyperthermia, hypovolemia, and in two cases, even more serious heat illness.

Because drinking water may acquire a bitter taste at high levels of pH (e.g., > 8.5)[2] and because pH adjustment, additional flavoring, odor control, and shading or mechanical chilling or cooling of warm water or even mechanical heating of very cold water to an optimum preferred temperature of 15°C (59°F) may not always be possible under battlefield conditions, we recommend the following research be performed. First, the spectrum of possible performance degrading effects that may affect military personnel forced to drink water at temperatures between a preferred 15°C (59°F) and a far less desireable 40°C (104°F) or at temperatures below 15°C (59°F) should be determined.

Second, the effect of pH in field water at levels above 8.5 and below 5 should be examined with respect to fluid consumption and the risk of dehydration. Third, field-water odor levels that are both acceptable and unacceptable to military personnel under combat conditions in hot, arid environments need to be identified more precisely. Finally, the synergistic effects related to temperature, pH, and odor on palatability/hydration, particularly during prolonged work in hot, arid environments should be studied so that impacts to operational effectiveness can be assessed when levels for these factors are not within tolerable limits.

TURBIDITY AND COLOR

Our review of the literature dealing with turbidity and color showed that neither property directly impacts health. However, turbidity composed of organic matter has been shown to decrease the efficiency of disinfection and hence increase exposure to pathogenic organisms. Because chlorine demand is directly related to organic turbidity, it could be used to determine whether turbid waters present a potential problem for effective disinfection. None of the work reviewed provides definitive results that can be used to refine field-water standards for turbidity or disinfection requirements when turbidity impairs disinfection efficiency. Accordingly, there are two important areas of research that should be pursued and both address the effect of turbidity on disinfection efficiency. First, studies are needed to define the relationships between the turbidity of various natural waters (measured by standard optical techniques as well as chemical analyses), the physical and chemical properties of the turbidity, chlorine demand, and the disinfection efficiency for pathogens that could be encountered in field waters. Once a better understanding of the interactions between these properties is obtained, more precise limits can be placed on turbidity (as currently measured) or more specific measures involving a characteristic of turbidity (e.g., wt% organic content) can be used to assess impacts of turbidity on disinfection. A second, related topic for research is the development of improved techniques for assessing in the field the chemical or physical characteristics of turbidity that can be used to identify conditions leading to decreased disinfection efficiency for specific pathogenic organisms.

Our analyses supporting the development of field-water standards for turbidity and color also focused on the degree to which these parameters would affect the willingness of field personnel to consume water that was turbid or that was colored. The concern here was with the potential for involuntary dehydration resulting from the reduced consumption of aesthetically poor water. We based the analyses on the work of Harris,[3] which indicated that a major portion of the population's acceptance of drinking water is

concerned with the three factors: color, turbidity, and odor. However, Harris's results were based on the responses from a civilian population in a relatively limited geographic area in Southern California as well as relatively few turbidity and color values covering an extensive range. These responses resulted in an inadequate representation of values at the low end of the color and turbidity scales. In spite of these shortcomings, Harris's[3] work represents a major step toward relating water acceptability to color, turbidity, and odor concentrations.

Research needs to be conducted with troops under actual field conditions (e.g., short-term [≤ 7 d] and longer term [~2 weeks] maneuvers under both temperate and hot conditions) to ascertain how field water with varying levels of turbidity and color influences water consumption. Moreover, for the sake of completeness, such research should relate the above properties not only to water consumption, but to measures of dehydration or heat stress as well. Results of these studies could be used to determine whether the recommended color standard of 50 color units for periods up to 7 days needs to be revised. Follow-on studies should investigate the effectiveness of different methods of dealing with water rejection, including mandatory drinking, special training, etc. Acclimation to colored and/or turbid water under field conditions has not been studied, and should be addressed also. Finally, water that is aesthetically displeasing because of color/turbidity and is also poor tasting because of dissolved solids represents another Research for addressing this problem is addressed below.

TOTAL DISSOLVED SOLIDS (TDS)

The concentration limit for TDS was established to prevent laxative effects and to minimize the fraction of exposed troops that would reject field water because of taste. One issue that needs to be addressed further with regard to TDS is the relationship between TDS and laxative effects. In particular, whether laxation is caused more by the combined action of all dissolved constituents, or the concentration of specific ions (e.g., Mg^{+2} and SO_4^{-2}). If TDS exerts significant laxative effects (e.g., because of the synergistic effect of individual ions), then a concentration-(dose)-response relationship should be determined, if possible, with human subjects. Otherwise, dose-response relationships need to be defined for the constituents that clearly can induce laxation.

With regard to the analysis based on organoleptic responses to field water with varying concentrations of TDS, additional research is needed to confirm whether or not the findings by Bruvold and Ongerth,[4] which indicate for the general population that psychometric ratings are not systematically affected by water temperature in the range of

40°F (4.5°C) to 72°F (22.3°C), are applicable to military populations, particularly those operating in hot, arid environments. Additional work also is needed to determine (1) why some mineral content in water is preferred to distilled water,[5-7] (2) how acclimation to a water supply would affect psychometric ratings, and (3) if the procedure developed by Bruvold and Gaffey[8] to derive a multiple regression equation for determining combinational effects of ions on ratings of water, could be adapted to reflect the contribution of the individual ions. Moreover, we recommend refining the experimental design of any additional taste-testing research. These refinements should include (1) the use of military personnel as subjects under actual field conditions so that the taste response of the population actually at risk could be determined more accurately; (2) the use of a large enough military population so that each subject would respond to only one type of water, thus enhancing the randomness of sampling and achieving a more representative response; (3) the introduction of some incentive or stress condition (e.g., slight dehydration, fatigue, etc., induced by simulated desert walk) so that military acceptability of drinking water under the pressures of combat-related situations could be ascertained; and (4) the determination of any negative synergism between TDS concentration and temperature of field water with respect to voluntary fluid consumption during work performed under hot weather conditions.

CHLORIDE

We used the linear regression equations of Bruvold and Ongerth,[4] which relate behavioral responses to the TDS of water, to develop chloride standards for military field-water supplies. The chloride limits were based on the assumption that chloride constituted 60% of the TDS concentration in field water. This assumption corresponds to the fact that chloride anions and sodium cations are predominant in field water processed by reverse osmosis water purification equipment. Additional research on behavioral responses to water containing chloride should be conducted. This research could be performed as part of the research recommended for TDS. Primarily, studies should be conducted with troops under actual field conditions to determine the nature and magnitude of responses to field waters of different chemical composition.

Furthermore, the standard for chloride ions in field water is recommended primarily because the total dissolved solids (TDS) content in product water from a reverse osmosis water purification unit (ROWPU) consists almost entirely of sodium (Na) and chloride (Cl) ions and elevated levels of chloride ions in drinking water can produce an objectionable taste. Therefore, a recommended standard for chloride ions of 600 mg/L corresponds to a NaCl concentration of approximately 1000 mg/L, which is also the concentration

recommended as the standard for TDS. However, the acceptability of the chloride standard is based on the assumption that ingestion of up to 1 g (1000 mg) of NaCl per litre of water consumed does not by itself pose a health risk. Nevertheless, if 15 L of water is consumed daily the additional amount of dietary salt ingested each day above that contained in military rations equates to nearly 15 g. According to the results of research by Dasler et al.,[9] Ladell,[10] and Knochel et al.[11] excessive salt loading over a 24 h period in hot environments may result in effects such as cardiovascular impairment, decreased work capacity, impaired heat acclimation, as well as cause gastrointestinal disturbances, aggravate dehydration, and contribute directly to rhabdomyolysis (i.e., destruction or weakening of skeletal muscle), potassium deficiency, and other heat injuries. Therefore the degree to which such effects might occur and be performance degrading in all or part of a military population eating adequate military rations and consuming up to 15 L/d of water containing a NaCl concentration of approximately 1 g/L needs to be investigated further. Such research can then be used to support or change the recommended standard for chloride in field water of 600 mg/L.

MAGNESIUM

The most important research for reducing the uncertainty in the recommended standard for magnesium would be to develop a dose-response curve for the laxative effects of magnesium ions and magnesium salts in drinking water. Other research should focus on the mechanism by which magnesium causes laxative effects. Issues that need to be answered include, "How seriously does magnesium's ability to reduce intestinal water absorption affect water balance in troops that drink mineralized water?" and "Can adaptation to magnesium's laxative effects be managed?" Additional research should address the organoleptic and behavioral responses to water containing varying levels of dissolved magnesium.

SULFATE

The primary health effect associated with the consumption of sulfate in field water is laxation. Our review of the available literature on the laxative effects of sulfate indicates that research is needed to define a dose-response function for the laxative effects of sulfates. This could be accomplished by experiments in which the potency of various sulfate salts (e.g., Na_2SO_4, $CaSO_4$ and $MgSO_4$) are examined. Such experiments would help establish the approximate potency of the sulfate ion and determine whether the various cations substantially mediate its laxative effects.

Additional studies could involve analysis of synthetic or natural high-sulfate waters with high levels of total dissolved solids. These studies could help evaluate the combinatorial effects of sulfate in the presence of other ions to determine if the sulfate level should be adjusted for the presence of other ions. Additional research is needed to elucidate the mechanism by which sulfate ions cause laxative effects. Specifically, how the laxative mechanism affects the absorbtion of water from the intestinal tract. Also of interest is the time it takes to acclimate to different levels of sulfate and whether acclimation to a water will persist for long periods of time. Research involving organoleptic and behavioral responses to sulfate-containing water should be done in conjuction with studies recommended earlier for TDS, chloride, and magnesium.

ARSENIC

Research to improve the recommended standard for arsenic should deal with the nature of delayed or subclinical neuropathies in populations exposed to elevated levels of arsenic in drinking water. To conduct such research it may also be necessary to develop sensitive techniques for detecting neuropathies associated with the ingestion of arsenic (i.e., both total and individual species). The results of this research would substantiate the standards we recommend for military personnel, or indicate necessary adjustments. This would be particularly helpful for the short-term (7d) standard where information is sparse on the human health effects caused by short-term exposure to arsenic in drinking water. One possible location for such a human health-effects study would be the Naval Air Station at Fallon, Nevada.[12,13] Troops there consume water reported to contain up to 100 µg/L (0.1 mg/L) of probably only pentavalent inorganic arsenic. The development of a field method to ascertain unusually high proportions of trivalent arsenic in water represents another area of future research. Such a method would help field personnel determine the relative toxicity of total arsenic in their water supply.

CYANIDE

A pharmacokinetic model was used to calculate oral doses of cyanide that would not produce blood cyanide concentrations above a no-effect level after several administrations. Parameter estimates for the absorption and elimination rate constants were based in part on human data involving individuals experiencing physiological stress - due either to an overdose of cyanide or administration of SNP, a drug containing cyanide and used to control blood pressure during surgery. Additional research is needed to more

accurately define inter-individual variation in key parameters such as the volume of distribution and fraction of ingested cyanide that is available for systemic circulation after first-pass detoxification in the liver. It may be possible to estimate the distribution volume from data obtained during studies in which patients received infusion of SNP, however, this needs to be investigated further. Measurements of the magnitude of first-pass detoxification as well as the rate constant for absorption should be the subject of experiments conducted with suitable animal species. Also of interest is the toxicological significance of cyanide in plasma, red blood cells, or whole blood. Specifically, which of the concentration measures correlates the best with toxic effects. Again, animal studies can be carried out to examine this question. One other important area of research concerns the extent to which unmetabolized cyanide is eliminated via sweat. If sweat is an important pathway of excretion, then the relationship between sweat losses and maximum water intake rate would have to be examined and perhaps adjusted. It is possible that experiments could be conducted with human subjects without administering cyanide because cyanide is a normal component of blood. Thus, if the detection limits for analyzing cyanide in blood and sweat were low enough, it would be possible to measure cyanide elimination in individuals who are perspiring at different rates.

LINDANE

The standard for lindane was based on assessments of available dose-response data for both humans and animals. Unfortunately, a threshold or no-effect dose has not been established for humans and so a safety factor was applied to animal dose-rate data to develop a standard. Further research on lindane should focus on the dose-response relationships for subtle neurological effects (abnormal EEG readings) that can occur from lindane intoxication. In this regard we recommend that research be directed toward the identification of suitable animal models for studying such effects.

ALGAE AND ASSOCIATED AQUATIC BACTERIA

A number of studies are needed to better establish the consequences of the presence of algal blooms in field-water supplies. First, research should be performed to establish the relationship between concentrations of the taste- and odor-producing substances geosmin and MIB released in field water, and the rejection of such water by military personnel. Currently, data only exist for geosmin and the response of the general public. Second, methods should be developed to correlate concentrations of cyanobacteria and

actinomycetes with the concentrations of the taste- and odor-producing metabolites they may release. This will permit estimation of the quantity of metabolites in field water that otherwise would require laboratory analysis to determine.

Another area of research concerns the toxic properties of cyanobacteria. The effects of individual toxins on human populations need to be established. This research will require identification and use of suitable animal models and the collection and analysis of epidemiological data from populations exposed to algal blooms in public drinking water supplies. The research should help determine the dose-response relationship for these biochemicals for humans. The pharmacology of all pertinent alkaloid, lipopolysaccharide, and polypeptide toxins also should be elucidated to establish their mode of action in cases of human poisonings, and the toxicity of these biochemicals with respect to performance degradation in military personnel. Possible synergisms between toxins should also be examined. Additionally, the relationship between the concentration of the taste- and odor-producing metabolites and the concentration of toxic substances in field water should be evaluated. Such a relationship would permit taste- and odor-producing metabolites to be used as indicators of the possible toxicity of field water. Finally, conditions promoting toxin formation by blue-green algae and release of taste- and odor-causing metabolites by algae and associated aquatic bacteria need to be determined.

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