Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate

Panel on Dietary Reference Intakes for Electrolytes and Water, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes

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Standing Committee on the Scientific Evaluation of Dietary Reference Intakes

Food and Nutrition Board

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Willing is not enough; we must do."
—Goethe

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Preface

This report is one in a series that presents a comprehensive set of reference values for nutrient intakes for healthy U.S. and Canadian individuals and populations. It is a product of the Food and Nutrition Board (FNB) of the Institute of Medicine, working in cooperation with Canadian scientists.

The report establishes a set of reference values for dietary electrolytes and water to expand and replace previously published Recommended Dietary Allowances (RDAs) and Recommended Nutrient Intakes (RNIs) for the United States and Canada, respectively. Close attention was given to the evidence relating electrolyte intake to the risk of high blood pressure and hypertension, as well as other diseases, and the amounts of water from beverages and foods needed to maintain hydration. In addition, since requirements for sulfur can be met by inorganic sulfate in the diets of animals, a review of the role in inorganic sulfur in the form of sulfate is included.

The group responsible for developing this report, the Panel on Dietary Reference Intakes for Electrolytes and Water, under the oversight and assistance of the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (the DRI Committee), has analyzed the evidence on risks and beneficial effects of nutrients included in this review.

Although all reference values are based on data, available data were often sparse or drawn from studies with significant limitations in addressing various questions confronted by the panel. Thus, although governed by scientific rationales, informed judgments were often required in setting these reference values. The reasoning used

in evaluating each nutrient is described in Chapters 4 through 7. Chapter 3 outlines the risk assessment approach used to establish the reference values for upper intake levels as developed and further modified by the DRI Subcommittee on Upper Reference Levels. Chapter 8 addresses major conceptual issues related to the uses of the DRIs that were included in the early stages of the DRI process and have been developed further as described in reports from the Subcommittee on Interpretation and Uses of Dietary Reference Intakes.

While the quantity of research reports relating sodium and potassium intake to blood pressure is quite large, the quality of the research useful to the panel for setting requirements of sodium and potassium was limited. In particular, there was a dearth of large, dose-response studies with clinically relevant biological outcomes carried out in normal, apparently healthy individuals.

Given the ability of many humans to adapt to varying amounts of electrolyte intake and the impact of temperature and activity level on needs of electrolytes and water, it was not possible to determine Estimated Average Requirements (EAR) for these nutrients. Instead, Adequate Intakes (AIs) were set for sodium, potassium, and water. No AI was set for sulfate as there is sufficient sulfur in the human diet from foods (derived from sulfur amino acids) and water to meet the needs of healthy individuals. No specific Tolerable Upper Intake Levels (ULs) were set for water, potassium, or sulfate as healthy persons can adapt to higher intakes from foods and beverages. In contrast, a UL was set for sodium based upon the increased risk of cardiovascular outcomes, particularly cardiovascular disease and stroke.

Readers are urged to recognize that the DRI process is iterative in character. The FNB and the DRI Committee and its subcommittees and panels fully expect that the DRI conceptual framework will evolve and be improved as novel information becomes available and is applied to an expanding list of nutrients and other food components. Thus because the DRI activity is ongoing, comments have been solicited widely and received on the published reports of this series. Refinements that resulted from this iterative process were included in the general information regarding approaches used (Chapters 1 and 2 and in the discussion of uses of DRIs in Chapter 8). With more experience, the proposed models for establishing reference intakes of nutrients and other food components that play significant roles in promoting and sustaining health and optimal functioning will be refined. Also, as new information or new meth-

ods of analysis are adopted, these reference values undoubtedly will be reassessed.

Many of the questions that were raised about requirements and recommended intakes could not be answered satisfactorily for the reasons given above. Thus among the panel's major tasks was to outline a research agenda addressing information gaps uncovered in its review (Chapter 9). The research agenda is anticipated to help future policy decisions related to these and future recommendations. This agenda and the critical, comprehensive analyses of available information are intended to assist the private sector, foundations, universities, governmental and international agencies and laboratories, and other institutions in the development of their respective research priorities for the next decade.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

> Michael Alderman, Albert Einstein College of Medicine; John R. Claybaugh, Tripler Army Medical Center; David Cole, University of Toronto; Gary Curhan, Harvard University; Johanna T. Dwyer, Tufts New England Medical Center; Shiriki K. Kumanyika, University of Pennsylvania; Gary W. Mack, Yale University; Melinda Manore, Oregon State University; Timothy Noakes, Sports Science Institute of South Africa; Suzanne Oparil, University of Alabama at Birmingham; Frank Sacks, Harvard University; Judith Stern, University of California at Davis.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by John W. Suttie, University of Wisconsin, appointed by the Institute of Medicine, who was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final

content of this report rests entirely with the authoring panel and the institution.

The support of the Canadian government and Canadian scientists' participation in this initiative are gratefully acknowledged. This close collaboration represents a pioneering first step in the harmonization of nutrient reference intakes in North America. A description of the overall DRI project and of the panel's task is given in Appendix B.

The DRI Committee and the Panel on DRIs for Electrolytes and Water extend sincere appreciation to the many experts who assisted with this report by giving presentations to the panel, providing written materials, participating in the groups' open discussions, analyzing data, reviewing the report, and other means. Many, but far from all, of these individuals are named in Appendix L. Special gratitude is extended to the staff at ENVIRON International Corporation for providing national survey data.

The Panel on DRIs for Electrolytes and Water performed their work under great time pressure. Their dedication made the report's completion possible. All gave their time and hard work willingly and without financial reward; the public and the science and practice of nutrition are among the major beneficiaries of their dedication. Special thanks go to DRI Committee members Robert Russell, Joseph Rodricks, and Susan Barr for assisting the Panel in its review. In addition, the DRI Committee thanks the staff responsible for its development—in particular Paula Trumbo who served as a program officer for the study through June 2003, Allison A. Yates, who stepped in as Paula's replacement, and Crystal Rasnake, research assistant on the project in the later phases of its completion and key to organizing the many references and tables. The intellectual and managerial contributions made by these individuals to the report's comprehensiveness and scientific base were critical to fulfilling the project's mandate. Sincere thanks also go to other FNB staff, including Carrie Holloway, Mary Poos, Gail Spears, and Sandra Amamoo-Kakra, who also contributed their efforts over the years to complete this document.

And last, but certainly not least, the DRI Committee wishes to extend special thanks to panel chair Larry Appel, who oversaw the entire report development process, to Vernon Young, past chair of the DRI Committee, and to Cutberto Garza, former Chair of the Food and Nutrition Board, under whom this study was initiated.

John Erdman
Chair, DRI Committee

Postscript:

Following release of the report in pre-publication copy form, the Panel and DRI Committee were saddened to learn of two untimely events: the deaths of both Lawrence M. Resnick, M.D., a member of the Panel who was steadfast in his views while congenial in his search for approaches that were scientifically supportable; and Vernon R. Young, Ph.D., who, as the first chair of the DRI Committee, led the pursuit of integrating good science into nutrient-based reference values while challenging all those involved to think past old axioms as the term "nutrient" was redefined; he was a true scholar.

Contents

DIETARY REFERENCE INTAKES

FOR

Water, Potassium, Sodium, Chloride, and Sulfate

Summary

This is one volume in a series of reports that presents dietary reference values for the intake of nutrients by Americans and Canadians. This report provides Dietary Reference Intakes (DRIs) for water, potassium, sodium, chloride, and sulfate.

The development of DRIs expands and replaces the series of reports called *Recommended Dietary Allowances* (RDAs) published in the United States and *Recommended Nutrient Intakes* (RNIs) in Canada. A major impetus for the expansion of this review is the growing recognition of the many uses to which RDAs and RNIs have been applied and the growing awareness that many of these uses require the application of statistically valid methods that depend on reference values other than RDAs or RNIs. This report includes a review of the roles that electrolytes and water are known to play in traditional deficiency states and diseases, as well as a discussion of their roles in the development of chronic diseases, and provides, where warranted, reference values for use in assessing and planning diets.

The overall project is a comprehensive effort undertaken by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (the DRI Committee) of the Food and Nutrition Board, Institute of Medicine, The National Academies, in collaboration with Health Canada (see Appendix B for a description of the overall process and its origins). This study was requested by the Federal Steering Committee for Dietary Reference Intakes, which is coordinated by the Office of Disease Prevention and Health Promotion of the U.S. Department of Health and Human Services, in collaboration with Health Canada.

Major findings in this report include the following:

- The establishment of Adequate Intakes (AIs) for *total* water (which includes drinking water and the water content of beverages and food), potassium, sodium, and chloride.
- The establishment of a Tolerable Upper Intake Level (UL) for sodium and chloride.
- Research recommendations for information needed to advance the understanding of human requirements for water and electrolytes as well as adverse effects associated with intakes of excessive amounts of water, sodium, chloride, potassium, and sulfate.

APPROACH FOR SETTING DIETARY REFERENCE INTAKES

The scientific data used to develop Dietary Reference Intakes (DRIs) have come primarily from observational and experimental studies conducted in humans. Studies published in peer-reviewed journals were the principal source of data. Life stage and gender were considered to the extent possible. Three of the categories of reference values—the Estimated Average Requirement (EAR), the Recommended Dietary Allowance (RDA), and the Adequate Intake (AI)—are defined by specific criteria of nutrient adequacy; the fourth, the Tolerable Upper Intake Level (UL), is defined by a specific endpoint of adverse effect, when one is available (see Chapter 1 for an overview of the approach).

In all cases, data were examined closely to determine whether a functional endpoint could be used as a criterion of adequacy. The quality of studies was examined by considering study design; methods used for measuring intake and indicators of adequacy; and biases, interactions, and confounding factors.

Although the reference values are based on data, the data were often scanty or drawn from studies that had limitations in addressing the various questions that confronted the panel. Therefore, many of the questions identified regarding the requirements for and recommended intakes of these electrolytes and of water cannot be answered fully because of inadequacies in the present database. Accordingly, a research agenda is proposed (see Chapter 9). In particular, there was a dearth of large, dose-response trials with clinically relevant biological outcomes (considered indicators of adequacy or excess). The absence of such studies is not unique to water and electrolytes. Rather, there are substantial feasibility considerations that preclude the conduct of such trials, especially when the

clinical outcome is a chronic disease. The reasoning used to establish the values is described for each nutrient reviewed in Chapters 4 through 7.

While the various recommendations are provided as single rounded numbers for practical considerations, it is acknowledged that these values imply a precision not fully justified by the underlying data from currently available human studies.

Box S-1 provides definitions of each of the categories of Dietary Reference Intakes applicable to electrolytes and water. To establish a Recommended Dietary Allowance (RDA), by definition it is necessary to be able to estimate an intake level that would meet the requirement of *half* of the individuals in the subgroup of the population for whom the recommendation is made; estimating this average requirement (EAR) requires that there be sufficient dose-response data relating intake to one or more criteria or functional endpoints that are reasonably sensitive to the presence or absence of the nutrient.

None of the nutrients reviewed in this report had sufficient dose-response data to be able to set an EAR, and from that derive an RDA. Thus, for each nutrient, with the exception of sulfate, an adequate intake (AI) is set. The indicators used to derive the AIs are

BOX S-1 Dietary Reference Intakes: Definitions

Recommended Dietary Allowance (RDA): *the average daily dietary nutrient intake level sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular life stage and gender group.*

Adequate Intake (AI): *the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate—used when an RDA cannot be determined.*

Tolerable Upper Intake Level (UL): *the highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects may increase.*

Estimated Average Requirement (EAR): *the average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group.*

described below. For sulfate, the scientific evidence was insufficient to set an AI. However, sulfate needs are met by the current recommended intakes for sulfur amino acids, which provide most of the inorganic sulfate needed for metabolism.

NUTRIENT FUNCTIONS AND THE INDICATORS USED TO ESTIMATE REQUIREMENTS

Water

The largest single constituent of the human body, water, is essential for cellular homeostasis and life. It provides the solvent for biochemical reactions, is the medium for material transport, and has unique physical properties (high specific heat) to absorb metabolic heat. Water is essential to maintain vascular volume, to support the supply of nutrients to tissues, and to remove waste via the cardiovascular system and renal and hepatic clearance. Body water deficits challenge the ability of the body to maintain homeostasis during perturbations (e.g., sickness, physical exercise, or climatic stress) and can impact function and health. *Total* water intake includes drinking water, water in other beverages, and water (moisture) in food (Table S-1).

Although a low intake of *total* water has been associated with some chronic diseases, this evidence is insufficient to establish water intake recommendations as a means of reducing the risk of chronic diseases. Instead, an AI for *total* water is set to prevent deleterious (primarily acute) effects of dehydration, which include metabolic and functional abnormalities.

Hydration status, as assessed by plasma or serum osmolality, is the primary indicator used for water. Physical activity and environmental conditions have substantial influences on water needs. Because of homeostatic responses, some degree of over- and underhydration can readily be compensated over the short term. While it might appear useful to estimate an average requirement (EAR) for water, it is not possible for a nutrient like water. Given the extreme variability in water needs that are not solely based on differences in metabolism, but also on environmental conditions and activity, there is not a single level of water intake that would ensure adequate hydration and optimal health for *half* of all apparently healthy persons in all environmental conditions. Hence, an EAR could not be established. Rather, an AI is established instead of an RDA, which must be derived from an EAR.

U.S. survey data from the Third National Health and Nutrition

TABLE S-1 Percent of Median *Total* Water Intake in the United States from Beverages (Including Drinking Water) and Food

Life Stage Group[a]	Percent from Beverages[b]	Percent from Foods
Both sexes, 0–6 mo	100	0
Both sexes, 7–12 mo	74	26
Both sexes, 1–3 y	71	29
Both sexes, 4–8 y	70	30
M, 9–13 y	76	24
M, 14–18 y	80	20
M, 19–30 y	81	19
M, 31–50 y	81	19
M, 51–70 y	81	19
M, > 70 y	81	19
F, 9–13 y	75	25
F, 14–18 y	80	20
F, 19–30 y	81	19
F, 31–50 y	81	19
F, 51–70 y	81	19
F, > 70 y	81	19
Pregnant	77	22
Lactating	82	18

[a] M = male, F = female.

[b] Includes drinking water.

SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey, 1988–1994.

Examination Survey (NHANES III) indicate that serum osmolality, an indicator of hydration status, is maintained at a constant level over a wide range of *total* water intakes (i.e., serum osmolality is nearly identical for individuals in the lowest decile of reported intake compared with those in the highest decile of intake). Based on these data, the AI for *total* water (from consuming a combination of drinking water, beverages, and food) is set based on the median *total* water intake from the U.S. NHANES III data (Table S-2). The AI for *total* water intake for young men and women (19 through 30 years) is 3.7 L and 2.7 L per day, respectively (see Table S-2).[1] In the NHANES, fluids (beverages and drinking water) provided approximately 3.0 L (101 fluid ounces; ≈ 13 cups) and 2.2 L (74 fluid

[1] Conversion factors: 1 L = 33.8 fluid oz; 1 L = 1.06 qt; 1 cup = 8 fluid oz.

TABLE S-2 Criteria and Dietary Reference Intake Values[a] for *Total* Water[b]

Life Stage Group	Criterion
0 through 6 mo	Average consumption of water from human milk
7 through 12 mo	Average consumption of water from human milk and complementary foods
1 through 3 y	Median total water intake from NHANES III
4 through 8 y	Median total water intake from NHANES III
9 through 13 y	Median total water intake from NHANES III
14 through 18 y	Median total water intake from NHANES III
> 19 y	Median total water intake from NHANES III
Pregnancy	
14 through 50 y	Same as median intake for nonpregnant women from NHANES III
Lactation	
14 through 50 y	Same as median intake for nonlactating women from NHANES III

[a] No Tolerable Upper Intake Level is established; however, maximal capacity to excrete excess water in individuals with normal kidney function is approximately 0.7 L/hour.

[b] *Total* water represents drinking water, water in other beverages, and water (moisture) from food. See Table S-1 for the median percent of *total* water intake from beverages (including drinking water) and from foods reported in the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994).

ounces; ≈ 9 cups) per day for 19- through 30-year-old men and women, representing ~ 81 percent of *total* water intake (Table S-1). Water contained in food provided ~ 19 percent of *total* water intake. Canadian survey data indicated somewhat lower levels of *total* water intake (Appendix F).

As with AIs for other nutrients, for a healthy person, daily consumption below the AI may not confer additional risk because wide ranges of intakes are compatible with normal hydration. In this setting, the AI should not be interpreted as a specific requirement. Higher intakes of *total* water will be required for those who are physically active or who are exposed to hot environments.

While over the course of a few hours body water deficits can occur due to reduced intake or increased water (sweat) losses from physi-

AI[c] (L/d)					
Male			Female		
From Foods	From Beverages	***Total* Water**	From Foods	From Beverages	***Total* Water**
0.0	0.7	**0.7**	0.0	0.7	**0.7**
0.2	0.6	**0.8**	0.2	0.6	**0.8**
0.4	0.9	**1.3**	0.4	0.9	**1.3**
0.5	1.2	**1.7**	0.5	1.2	**1.7**
0.6	1.8	**2.4**	0.5	1.6	**2.1**
0.7	2.6	**3.3**	0.5	1.8	**2.3**
0.7	3.0	**3.7**	0.5	2.2	**2.7**
			0.7	2.3	**3.0**
			0.7	3.1	**3.8**

[c] AI = Adequate Intake. The observed average or experimentally determined intake by a defined population or subgroup that appears to sustain a defined nutritional status, such as growth rate, normal circulating nutrient values, or other functional indicators of health. The AI is used if sufficient scientific evidence is not available to derive an Estimated Average Requirement. **The AI is not equivalent to a Recommended Dietary Allowance.**

cal activity and environmental (e.g., heat) exposure, on a day-to-day basis fluid intake, driven by the combination of thirst and the consumption of beverages at meals, allows maintenance of hydration status and total body water at normal levels.

Approximately 80 percent of *total* water intake comes from drinking beverages and water. While consumption of beverages containing caffeine and alcohol have been shown in some studies to have diuretic effects, available information indicates that this may be transient in nature, and that such beverages contribute to *total* water intake.

While the AI is given in terms of *total* water, there are multiple sources of such water, including moisture content of foods, beverages such as juices and milk, and drinking water. While all of these

can contribute to meeting the adequate intake, no one source is essential for normal physiological function and health.

Potassium

The major intracellular cation in the body, potassium is required for normal cellular function. Severe potassium deficiency is characterized by hypokalemia—a serum potassium concentration of less than 3.5 mmol/L. The adverse consequences of hypokalemia include cardiac arrhythmias, muscle weakness, and glucose intolerance. Moderate potassium deficiency, which typically occurs without hypokalemia, is characterized by increased blood pressure, increased salt sensitivity,[2] an increased risk of kidney stones, and increased bone turnover (as indicated by greater urinary calcium excretion and biochemical evidence of reduced bone formation and increased bone resorption). An inadequate intake of dietary potassium may also increase the risk of cardiovascular disease, particularly stroke.

The adverse effects of inadequate potassium intake can result from a deficiency of potassium *per se*, a deficiency of its conjugate anion, or both. In unprocessed foods, the conjugate anions of potassium are organic anions, such as citrate, that are converted in the body to bicarbonate. Acting as a buffer, bicarbonate neutralizes diet-derived acids such as sulfuric acid generated from sulfur-containing amino acids commonly found in meats and other high protein foods. In the setting of an inadequate intake of bicarbonate precursors, buffers in the bone matrix neutralize excess acid and in the process bone becomes demineralized. Increased bone turnover and calcium-containing kidney stones are the resulting adverse consequences.

In processed foods to which potassium has been added and in supplements, the conjugate anion is typically chloride, which does not act as a buffer. Because the demonstrated effects of potassium often depend on the accompanying anion and because it is difficult to separate the effects of potassium from the effects of its accompanying anion, this evaluation focuses on research pertaining to non-

[2] In general terms, salt sensitivity is the extent of blood pressure change in response to a change in salt intake. Salt sensitivity differs among subgroups of the population and among individuals within a subgroup. The term "salt sensitive blood pressure" applies to those individuals or subgroups that experience the greatest change in blood pressure from a given change in salt intake—that is, the greatest reduction in blood pressure when salt intake is reduced.

chloride forms of potassium—the forms found naturally in fruits, vegetables, and other potassium-rich foods.

An EAR could not be set for potassium because the data currently available do not provide multiple dose levels within the range to determine the point at which the diet of approximately *half* of those evaluated would be inadequate for potassium. Thus an AI is given. The AI for potassium is set at 4.7 g (120 mmol) per day for adults (see Table S-3). Available evidence indicates that this level of potassium intake should lower blood pressure, blunt the adverse effects of sodium chloride on blood pressure, reduce the risk of kidney stones, and possibly reduce bone loss. It is important to note that the beneficial effects of potassium in these studies appear to be mainly from the forms of potassium that are associated with bicarbonate precursors—the forms found naturally in foods such as fruits and vegetables.

At present, dietary intakes of potassium by all groups in the United States and Canada are considerably lower than the AI. In recent surveys, the median intake of potassium by adults in the United States was approximately 2.9 to 3.2 g[3] (74 to 82 mmol)/day for men and 2.1 to 2.3 g (54 to 59 mmol)/day for women; in Canada, the median intakes ranged from 3.2 to 3.4 g (82 to 87 mmol)/day for men and 2.4 to 2.6 g (62 to 67 mmol)/day for women. Because African Americans have lower intakes of potassium and a higher prevalence of elevated blood pressure and salt sensitivity, this subgroup of the population would especially benefit from an increased intake of potassium.

It should be noted that individuals with chronic renal insufficiency, who may be taking angiotensin-converting enzyme (ACE) inhibitors, certain diuretics, individuals with type 1 diabetes, and those taking cyclo-oxygenase-2 (COX 2) inhibitors or other nonsteroidal anti-inflammatory (NSAID) drugs, should consume levels of potassium recommended by their health care professional, which may well be lower than the AI.

Sodium Chloride

Sodium and chloride are normally found together in most foods as sodium chloride, also termed salt. For that reason, this report presents data on the requirements for and the effects of sodium and

[3] To convert g of potassium to mmol of potassium, divide g by 39.1 (the molecular weight of potassium) and multiply by 1,000.

TABLE S-3 Criteria and Dietary Reference Intake Values[a] for Potassium by Life Stage Group

		AI (g/day)[b]	
Life Stage Group	Criterion	Male	Female
0 through 6 mo	Average consumption of potassium from human milk	0.4	0.4
7 through 12 mo	Average consumption of potassium from human milk and complementary foods	0.7	0.7
1 through 3 y	Extrapolation of adult AI based on energy intake	3.0	3.0
4 through 8 y	Extrapolation of adult AI based on energy intake	3.8	3.8
9 through 13 y	Extrapolation of adult AI based on energy intake	4.5	4.5
14 through 18 y	Extrapolation of adult AI based on energy intake	4.7	4.7
> 18 y	Intake level to lower blood pressure, reduce the extent of salt sensitivity, and to minimize the risk of kidney stones in adults	4.7	4.7
Pregnancy			
14 through 50 y	Intake level to lower blood pressure, reduce the extent of salt sensitivity, and to minimize the risk of kidney stones in nonpregnant adults		4.7
Lactation			
14 through 50 y	Intake level to lower blood pressure, reduce the extent of salt sensitivity, and to minimize the risk of kidney stones in nonlactating adults plus the average amount of potassium estimated in breast milk during the first 6 months (0.4 g/d)		5.1

[a] No Tolerable Upper Intake Level is established; however, caution is warranted given concerns about adverse effects when consuming excess amounts of potassium from potassium supplements while on drug therapy or in the presence of undiagnosed chronic disease.

[b] AI = Adequate Intake. The observed average or experimentally determined intake by a defined population or subgroup that appears to sustain a defined nutritional status, such as growth rate, normal circulating nutrient values, or other functional indicators of health. The AI is used if sufficient scientific evidence is not available to derive an Estimated Average Requirement. **The AI is not equivalent to a Recommended Dietary Allowance.**

chloride together.[4] Sodium and chloride are required to maintain extracellular fluid volume and serum osmolality. Human populations have demonstrated the capacity to survive at extremes of sodium intake from less than 0.2 g (10 mmol)/day of sodium in the Yanomamo Indians of Brazil to more than 10.3 g (450 mmol)/day in Northern Japan. The ability to survive at extremely low levels of sodium intake reflects the capacity of the normal human body to conserve sodium by markedly reducing losses of sodium in urine and sweat.

Under conditions of maximal adaptation and without sweating, the minimal amount of sodium required to replace losses is estimated to be no more than 0.18 g (8 mmol)/day. Still, it is unlikely that a diet providing this level of sodium intake is sufficient to meet dietary requirements for other nutrients. Given that dose-response data are lacking regarding the level of sodium and chloride intake from currently available foods in the United States and Canada at which *half* of the individuals in a group would have their needs met for other essential nutrients (which would be necessary to develop an EAR), an AI was developed instead.

The AI for sodium is set for young adults at 1.5 g (65 mmol)/day (3.8 g of sodium chloride) to ensure that the overall diet provides an adequate intake of other important nutrients and to cover sodium sweat losses in unacclimatized individuals who are exposed to high temperatures or who become physically active as recommended in other DRI reports. This AI does not apply to individuals who lose large volumes of sodium in sweat, such as competitive athletes and workers exposed to extreme heat stress (e.g., foundry workers and fire fighters). Sodium intake invariably rises with increased energy intake in physically active individuals, and this increase usually is enough to compensate for sweat sodium losses. However, some individuals in the situations described above can lose excessively large amounts of sodium in sweat, and on those occasions they should ingest a diet that contains sodium in excess of the AI.

The AI for sodium for older adults and the elderly is somewhat less, based on lower energy intakes, and is set at 1.3 g (55 mmol)/day for men and women 50 through 70 years of age, and at 1.2 g (50 mmol)/day for those 71 years of age and older (see Table S-4).

[4] In view of the format of published data, this report presents intake data primarily as g (mmol)/day of sodium and of chloride, rather than g (mmol)/day of sodium chloride (salt). To convert mmol to mg of sodium, chloride, or of sodium chloride, multiply mmol by 23, 35.5, or 58.5 (the molecular weights of sodium, chloride, and sodium chloride), respectively.

TABLE S-4 Criteria and Dietary Reference Intake Values for Sodium and Chloride

Life Stage Group	Criterion for AI for Sodium
0 through 6 mo	Average consumption of sodium from human milk
7 through 12 mo	Average consumption of sodium from human milk and complementary foods
1 through 3 y	Extrapolation of adult AI based on energy intake
4 through 8 y	Extrapolation of adult AI based on energy intake
9 through 13 y	Extrapolation of adult AI based on energy intake
14 through 18 y	Extrapolation of adult AI based on energy intake
19 through 50 y	Intake level to cover possible daily losses, provide adequate intakes of other nutrients, and maintain normal function
51 though 70 y	Extrapolated from younger adults based on energy intake
> 70 y	Extrapolated from younger adults based on energy intake
Pregnancy	
14 through 50 y	Same as for nonpregnant women
Lactation	
14 through 50 y	Same as for nonlactating women

[a] AI = Adequate Intake. The observed average or experimentally determined intake by a defined population or subgroup that appears to sustain a defined nutritional status, such as growth rate, normal circulating nutrient values, or other functional indicators of health. The AI is used if sufficient scientific evidence is not available to derive an Estimated Average Requirement. **The AI is not equivalent to a Recommended Dietary Allowance.**

Concerns have been raised that a low level of sodium intake adversely affects blood lipids, insulin resistance, and cardiovascular disease risk. However, at the level selected for the AI, the preponderance of evidence does not support this contention. A potential indicator of an adverse effect of inadequate sodium is an increase in plasma renin activity. However, in contrast to the well-accepted benefits of blood pressure reduction, the clinical relevance of modest rises in plasma renin activity as a result of sodium reduction is uncertain.

The AI for chloride is set at a level equivalent on a molar basis to that of sodium, since almost all dietary chloride comes with the sodium added during processing or consumption of foods. For example, the AI for chloride for younger adults is 2.3 g (65 mmol)/day of chloride, which is equivalent to 3.8 g/day of sodium chloride.

Sodium AI[a] (g/d)		Chloride AI[b] (g/d)		Sodium UL[c] (g/d)		Chloride UL[b] (g/d)	
Male	Female	Male	Female	Male	Female	Male	Female
0.12	0.12	0.18	0.18	ND[d]	ND	ND	ND
0.37	0.37	0.57	0.57	ND	ND	ND	ND
1.0	1.0	1.5	1.5	1.5	1.5	2.3	2.3
1.2	1.2	1.9	1.9	1.9	1.9	2.9	2.9
1.5	1.5	2.3	2.3	2.2	2.2	3.4	3.4
1.5	1.5	2.3	2.3	2.3	2.3	3.6	3.6
1.5	1.5	2.3	2.3	2.3	2.3	3.6	3.6
1.3	1.3	2.0	2.0	2.3	2.3	3.6	3.6
1.2	1.2	1.8	1.8	2.3	2.3	3.6	3.6
	1.5		2.3		2.3		3.6
	1.5		2.3		2.3		3.6

[b] Chloride determined on molar basis equal to sodium AI or UL.

[c] UL = Tolerable Upper Intake Level. Based on prevention of increased blood pressure.

[d] ND=Not determined. Intake should be from food or formula only.

Sulfate. This nutrient is required by the body for synthesis of 3′-phosphoadenosine-5′-phosphosulfate (PAPS), which in turn is used for synthesis of many important sulfur-containing compounds such as chondroitin sulfate and cerebroside sulfate. While substantial levels of sulfate are found in foods and various sources of drinking water, the major source of inorganic sulfate for humans is from body protein turnover of the sulfur amino acids, methionine and cysteine. Dietary inorganic sulfate in food and water, together with sulfate derived from methionine and cysteine found in dietary protein, as well as the cysteine component of glutathione, provide sulfate for use in PAPS biosynthesis. Sulfate requirements are thus met when intakes include recommended levels of sulfur amino acids. For this reason, neither an Estimated Average Requirement (and thus a Recommended Dietary Allowance) nor an Adequate Intake of sulfate is established.

CRITERIA AND PROPOSED VALUES FOR TOLERABLE UPPER INTAKE LEVELS

A risk assessment model is used to derive Tolerable Upper Intake Levels (ULs). The model consists of a systematic series of scientific considerations and judgments (see Chapter 3). The hallmark of the risk assessment model is the requirement to be explicit in all of the evaluations and judgments made.

Water

Water intoxication can lead to life-threatening hyponatremia, which can result in central nervous system edema, lung congestion, and muscle weakness. Hyponatremia occurs occasionally in psychiatric patients (psychogenic polydipsia). In unusual circumstances, hyponatremia can also occur from excessive fluid intake, underreplacement of sodium, or both during or after prolonged endurance athletic events. The symptomatic hyponatremia of exercise is typically associated with greater than 6 hours of prolonged stressful exercise. Acute water toxicity has been reported due to rapid consumption of large quantities of fluids that greatly exceeded the kidney's maximal excretion rate of from 0.7 to 1.0 L/hour. Hyponatremia does not occur in healthy populations consuming the average North American diet.

Thus, while hazards associated with overconsumption of fluid can be identified, there is no evidence that habitual consumption of a high *total* water intake results in identifiable hazards in apparently healthy people. Because of the ability to self regulate water intake from fluids and foods by healthy people in temperate climates, a Tolerable Upper Intake Level (UL) was not set for water.

Potassium

Gastrointestinal discomfort and ulceration of the gastrointestinal tract have been reported with excess consumption of some forms of potassium supplements but not with potassium from the diet. Cardiac arrhythmias from hyperkalemia are the most serious consequence of excessive potassium intake. The typical sequence of findings is hyperkalemia, followed by conduction abnormalities apparent from electroencephalograms, and then cardiac arrhythmias, which can be life-threatening. Such consequences result from either a high plasma concentration of potassium or from rapid and extreme changes in its concentration.

In individuals whose urinary potassium excretion is impaired by a medical condition, drug therapy, or both, instances of life-threatening hyperkalemia have been reported. However, in otherwise healthy individuals (that is, individuals without impaired urinary potassium excretion from a medical condition or drug therapy), there have been no reports of hyperkalemia resulting from acute or chronic ingestion of potassium naturally occurring in food. Therefore, a UL for potassium from foods is not set for healthy adults.

In contrast, excess consumption of supplemental potassium can lead to acute toxicity in healthy individuals. Also, chronic consumption of a high level of potassium can lead to hyperkalemia in individuals with impaired urinary potassium excretion. Hence, supplemental potassium should only be provided under medical supervision because of the well-documented potential for toxicity. Clinical settings in which high intakes of potassium could pose a serious risk include type 1 diabetes, chronic renal insufficiency, end-stage renal disease, severe heart failure, and adrenal insufficiency. In individuals with these diseases or clinical conditions, a potassium intake below the AI is often appropriate. For these individuals, salt substitutes (potassium chloride) should be used only under medical supervision.

Sodium Chloride

The main adverse effect of increased sodium chloride in the diet is increased blood pressure, which is a major risk factor for cardiovascular-renal diseases. Results from the most rigorous dose-response trials have documented a progressive, direct effect of dietary sodium intake on blood pressure in nonhypertensive as well as hypertensive individuals. The dose-dependent rise in blood pressure appears to occur throughout the spectrum of sodium intake. However, the relationship is nonlinear in that the blood pressure response to changes in sodium intake is greater at sodium intakes below 2.3 g (100 mmol)/day than above this level.

The strongest dose-response evidence comes from those clinical trials that specifically examined the effects of at least three levels of sodium intake on blood pressure. The range of sodium intakes in these studies varied from 0.23 g (10 mmol)/day to 34.5 g (1,500 mmol)/day. Several trials included sodium intake levels close to 1.5 g (65 mmol)/day and 2.3 g (100 mmol)/day.

While blood pressure, on average, rises with increased sodium intake, there is well-recognized heterogeneity in the blood pressure

response to changes in sodium chloride intake. Individuals with hypertension, diabetes, and chronic kidney disease, as well as older-age persons and African Americans, tend to be more sensitive to the blood pressure raising effects of sodium chloride intake than their counterparts. Genetic factors also influence the blood pressure response to sodium chloride.

There is considerable evidence that salt sensitivity is modifiable. The rise in blood pressure from increased sodium chloride intake is blunted in the setting of a diet high in potassium or a low-fat, mineral-rich diet; nonetheless, a dose-response relationship between sodium intake and blood pressure still persists. In nonhypertensive individuals, a reduced salt intake can decrease the risk of developing hypertension.

The adverse effects of higher levels of sodium intake on blood pressure provide the scientific rationale for setting the UL. Because the relationship between sodium intake and blood pressure is progressive and continuous without an apparent threshold, it is difficult to precisely set a UL, especially because other environmental factors (weight, exercise, potassium intake, dietary pattern, and alcohol intake) and genetic factors also affect blood pressure. For adults, a UL for sodium of 2.3 g (100 mmol)/day is set, equivalent to a total of 5.8 g/day of sodium chloride. In dose-response trials, this level was commonly the next level above the AI that was tested. The equivalent UL for chloride is 3.5 g. It should be noted that the UL is not a recommended intake and, as with other ULs, there is no demonstrated benefit to consuming levels above the AI.

Among certain groups of individuals who are most sensitive to the blood pressure effects of increased sodium intake (e.g., older persons, African Americans, and individuals with hypertension, diabetes, or chronic kidney disease), their UL for sodium may well be lower. These groups also experience an especially high incidence of blood pressure-related cardiovascular disease. In contrast, for individuals who are unacclimatized to prolonged physical activity in a hot environment, their needs may exceed the UL because of sodium sweat losses.

Sulfate

While diarrhea can occur from a high sulfate intake, this condition usually results from ingestion of water with high sulfate content. Overall, there were insufficient data to use the model of risk assessment to set a UL for sulfate.

Summary

Although a specific UL was not set for water, potassium, or sulfate, the absence of definitive data does not indicate that all people can tolerate chronic intakes of these substances at high levels. Like all chemical agents, nutrients and other food components can produce adverse effects if intakes are excessive. Therefore, when data are extremely limited or conflicting, extra caution may be warranted in consuming levels significantly above that found in typical food-based diets.

USING DIETARY REFERENCE INTAKES TO ASSESS NUTRIENT INTAKES OF INDIVIDUALS

Suggested uses of Dietary Reference Intakes (DRIs) appear in Box S-2. For statistical reasons that were addressed in the reports *Dietary Reference Intakes: Applications in Dietary Assessment* (IOM, 2000) and *Dietary Reference Intakes: Applications in Dietary Planning* (IOM, 2003) and described briefly in Chapter 8, when a Recommended Dietary Allowance (RDA) is not available for a nutrient, the Adequate Intake (AI) is the appropriate reference intake value to use in assessing and planning the nutrient intake of individuals. Usual intake at or above the AI has a low probability of inadequacy.

When the median intake of a population group is equal to or exceeds the AI, the prevalence of inadequacy is likely to be low, especially when the AI is set at the median intake of a healthy group. This is the case for *total* water, in which the AI was based on median intakes of a population with little evidence of chronic dehydration. In the case of potassium, where the AI is set at a level much higher than the median intake, it is not possible to estimate the prevalence of inadequacy from survey data. It is only possible to assume that those whose intakes from food are above the AI are consuming sufficient potassium. It isn't possible to speculate on the extent of inadequacy in those whose intakes are below the AI for potassium.

Chronic consumption above the UL may place an individual or group at risk of adverse effects. Therefore, the percent of survey individuals whose intakes exceeded the UL equals the percent of individuals whose diets would be considered excessive in that particular nutrient. For example, sodium intake data from the NHANES III (Appendix D), which collected 24-hour diet recalls for 1 or 2 days, indicate that:

BOX S-2 Uses of Dietary Reference Intakes for Healthy Individuals and Groups

Type of Use	*For an Individual*[a]	*For a Group*[b]
Assessment	**EAR:** use to examine the probability that usual intake is inadequate (if individual's usual intake is at the EAR, then 50% probability that intake is inadequate).	**EAR:** use to estimate the prevalence of inadequate intakes within a group (% in a group whose intakes are inadequate = % whose intakes are below the EAR).
	RDA: usual intake at or above this level has a low probability of inadequacy.	**RDA:** do not use to assess intakes of groups.
	AI[c]**:** usual intake at or above this level has a low probability of inadequacy.	**AI**[c]**:** mean usual intake at or above this level implies a low prevalence of inadequate intakes.
	UL: usual intake above this level may place an individual at risk of adverse effects from excessive nutrient intake.	**UL:** use to estimate the percentage of the population at potential risk of adverse effects from excess nutrient intake.

• The vast majority (between 95 and 99 percent) of men and women in the United States consumed dietary sodium at levels greater than the AI, and thus one would assume that intakes were "adequate," and thus sufficient to cover sodium losses.

• More than 95 percent of men and 75 percent of women in the United States had sodium intakes that exceeded the UL, even when the amount of sodium added to foods during meals (table salt) was excluded. In phase I of the same survey (NHANES III), 24.7 percent of men and 24.3 percent of women 18 years and older had

Type of Use	*For an Individual*[a]	*For a Group*[b]
Planning	**RDA:** aim for this intake.	**EAR:** use to plan an intake distribution with a low prevalence of inadequate intakes.
	AI[c]**:** aim for this intake.	**AI**[c]**:** use to plan mean intakes.
	UL: use as a guide to limit intake; chronic intake of higher amounts may increase the potential risk of adverse effects.	**UL:** use to plan intake distributions with a low prevalence of intakes potentially at risk of adverse effects.

RDA = Recommended Dietary Allowance
EAR = Estimated Average Requirement
AI = Adequate Intake
UL = Tolerable Upper Intake Level

[a] Evaluation of true status requires clinical, biochemical, and anthropometric data.
[b] Requires statistically valid approximation of distribution of usual intakes.
[c] For the nutrients in this report, AIs are set for all age groups for water, potassium, and sodium (and chloride on an equimolar basis to sodium). The AI may be used as a guide for infants as it reflects the average intake from human milk. Infants consuming formulas with the same nutrient composition as human milk are consuming an adequate amount after adjustments are made for differences in bioavailability. In the context of assessing groups, when the AI for a nutrient is not based on mean intakes of a healthy population, this assessment is made with less confidence. The use of other DRIs (the Estimated Energy Requirement [EER] and the Acceptable Macronutrient Distribution Range [AMDR]) are described in another report in this series (IOM, 2002/2005).

hypertension—while a multifactoral diagnosis, hypertension is causally related to increased sodium intake.

RESEARCH RECOMMENDATIONS

Three major types of information gaps were noted: (1) a paucity of data for estimating average requirements for electrolytes and water in presumably healthy humans; (2) an even greater dearth of

evidence on the electrolyte and water needs in infants, children, adolescents, the elderly, and pregnant and lactating women; and (3) a lack of multidose trials to determine the effects of electrolyte and water intake on chronic diseases. There is also a need for research on public health strategies that effectively reduce sodium intake and increase potassium intake in the general population.

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1

Introduction to Dietary Reference Intakes

Dietary Reference Intakes (DRIs) comprise a set of nutrient-based reference values, each of which has special uses. The development of DRIs expands on two series of reports, the *Recommended Dietary Allowances*, which have been published since 1941 by the National Academy of Sciences, and the *Recommended Nutrient Intakes* of Canada. This comprehensive effort is being undertaken by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board, Institute of Medicine of the National Academies, with the active involvement of Health Canada. See Appendix B for a description of the overall process and its origins.

WHAT ARE DIETARY REFERENCE INTAKES?

The reference values, collectively called the Dietary Reference Intakes (DRIs), include the Estimated Average Requirement (EAR), the Recommended Dietary Allowance (RDA), the Adequate Intake (AI), and the Tolerable Upper Intake Level (UL).

A requirement is defined as the lowest continuing intake level of a nutrient that will maintain a defined level of nutriture in an individual. The chosen criteria of nutritional adequacy are identified in each chapter; note that the criterion used may differ for individuals at different life stages. Hence, particular attention is given throughout this report to the choice and justification of each criterion used to establish requirement values.

This approach differs somewhat from that used by the Expert Consultation on *Trace Elements in Human Nutrition and Health* (WHO, 1996) of the World Health Organization (WHO), Food and Agriculture Organization (FAO), and International Atomic Energy Agency (IAEA). That report uses the term *basal requirement* to indicate the level of intake needed to prevent pathologically relevant and clinically detectable signs of a dietary inadequacy. The term *normative requirement* in that report indicates the level of intake sufficient to maintain a desirable body store or reserve. In this report, in developing RDAs and AIs, emphasis is placed instead on the reasons underlying the choice of the criteria of nutritional adequacy used to establish requirements. They are not designated as basal or normative.

Unless otherwise stated, all values given for EARs, RDAs, and AIs represent the quantity of the nutrient or food component to be supplied by foods from diets similar to those consumed in Canada and the United States. If the food source of a nutrient is very different (as in diets of some ethnic groups) or if the source is supplements, adjustments may have to be made for differences in nutrient bioavailability. When this is an issue, it is discussed for the specific nutrient in the section "Special Considerations."

RDAs and AIs are levels of intake recommended for individuals. They should reduce the risk of developing a condition that is associated with the nutrient in question and that has a negative functional outcome. The DRIs apply to the apparently healthy general population. Meeting the recommended intakes for the nutrients would not necessarily provide enough for individuals who are already malnourished, nor would they be adequate for certain disease states marked by increased nutritional requirements. Qualified medical and nutrition personnel must tailor recommendations for individuals who are known to have diseases that greatly increase nutritional requirements or who are at risk for developing adverse effects associated with higher intakes. Although the RDA or AI may serve as the basis for such guidance, qualified personnel should make necessary adaptations for specific situations

CATEGORIES OF DIETARY REFERENCE INTAKES

Each type of Dietary Reference Intake (DRI) refers to average daily nutrient intake of individuals over time. In most cases, the amount taken from day to day may vary substantially without ill effect.

Recommended Dietary Allowance

The *Recommended Dietary Allowance* (RDA) is the average daily dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular life stage and gender group (see Figure 1-1). The RDA is intended to be used as a goal for daily intake by individuals. The process for setting the RDA is described below; it depends on being able to set an Estimated Average Requirement (EAR). That is, if an EAR cannot be set, no RDA will be set.

Estimated Average Requirement

The *Estimated Average Requirement* (EAR) is the daily intake value that is estimated to meet the requirement, as defined by the specified indicator or criterion of adequacy, of half of the apparently healthy individuals in a life stage or gender group (see Figure 1-1). A normal or symmetrical distribution (median and mean are simi-

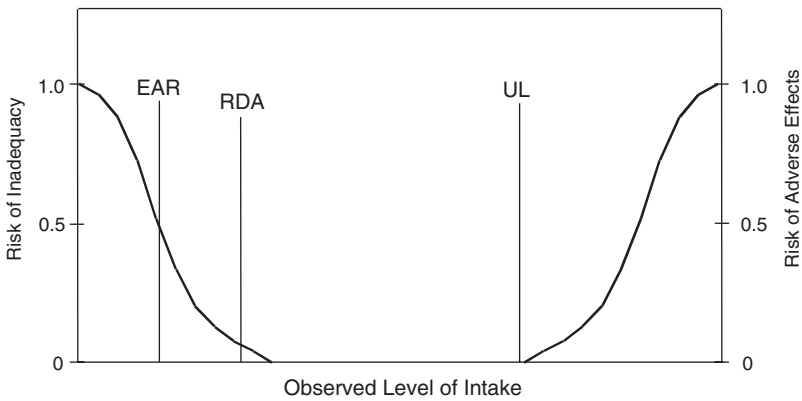

FIGURE 1-1 Dietary reference intakes. This figure shows that the Estimated Average Requirement (EAR) is the intake at which the risk of inadequacy is 0.5 (50 percent) to an individual. The Recommended Dietary Allowance (RDA) is the intake at which the risk of inadequacy is very small—only 0.02 to 0.03 (2 to 3 percent). **The Adequate Intake (AI) does not bear a consistent relationship to the EAR or the RDA because it is set without the estimate of the requirement.** At intakes between the RDA and the Tolerable Upper Intake Level (UL), the risks of inadequacy and of excess are both close to 0. At intakes above the UL, the risk of adverse effects may increase.

lar) is usually assumed for nutrient requirements. At this level of intake, half of the members of a specified group would not have their nutritional needs met. The general method used to set the EAR is the same for all the nutrients. For many of the nutrients, including those in this report, there are few direct data on the requirements of children. Thus, for such nutrients, EARs and RDAs for children are based on extrapolations from adult values. The methods used for extrapolation are described in Chapter 2.

Method for Setting the RDA When Nutrient Requirements Are Normally Distributed

If the requirement for the nutrient is normally distributed, and the standard deviation (SD) of the EAR is available, the RDA is defined as equal to the EAR plus 2 SDs of the EAR:

$$\text{RDA} = \text{EAR} + 2\ \text{SD}_{\text{EAR}}.$$

If data about variability in requirements are insufficient to calculate an SD, a coefficient of variation (CV_{EAR}) of 10 percent will be ordinarily assumed and used to estimate the SD:

$$\text{CV}_{\text{EAR}} = \text{SD}_{\text{EAR}}/\text{EAR}$$

and

$$\text{SD} = (\text{EAR} \times \text{CV}_{\text{EAR}}).$$

The resulting equation for the RDA is

$$\text{RDA} = \text{EAR} + 2\ (0.1 \times \text{EAR})$$

or

$$\text{RDA} = 1.2 \times \text{EAR}.$$

The assumption of a 10 percent CV is based on extensive data on the variation in basal metabolic rate (FAO/WHO/UNA, 1985; Garby and Lammert, 1984), which contributes about two-thirds of the daily energy needs of many individuals residing in Canada and the United States (Elia, 1992), and on the similar CV of 12.5 percent estimated for the protein requirements in adults (FAO/WHO/UNA, 1985).

Method for Setting the RDA When Nutrient Requirements Are Not Normally Distributed

When factorial modeling is used to estimate the distribution of requirements from the distributions of the individual components of requirement (e.g., losses, accretion), it is necessary to add the individual distributions. For normal component distributions, this is straightforward since the resultant distribution is also normal, with a mean that is the sum of the component means and a variance (the square of the SD) that is the sum of the individual variances. The ninety-seventh and one-half percentile is then estimated as the mean value plus two SDs.

If the requirement of a nutrient is not normally distributed but can be transformed to normality, its EAR and RDA can be estimated by transforming the data, calculating a fiftieth and a ninety-seventh and one-half percentile, and transforming these percentiles back into the original units. In this case, the difference between the EAR and the RDA cannot be used to obtain an estimate of the CV because skewing is usually present.

If normality cannot be assumed for all of the components of requirement, then Monte Carlo simulation is used for the summation of the components. This approach involves simulation of a large population of individuals (e.g., 100,000) each with his or her own requirement for a particular nutrient. To accomplish this, the component parts of nutrient needs (the factorial components) are treated as coming from independent random distributions.

For example, for basal losses of a nutrient, a distribution of expected losses can be generated. For each individual in the simulated population, a randomly selected basal loss value was drawn from that distribution of nutrient losses. This is done for each component of nutrient need and then these components are summed for each individual yielding the simulated nutrient needs. The total requirement is then calculated for each individual and the median and the ninety-seventh and one-half percentile calculated directly.

Information about the distribution of values for the requirement components is modeled on the basis of known physiology. Monte Carlo approaches may be used in the simulation of the distribution of components; or, where large data sets exist for similar populations (such as growth rates in infants), estimates of relative variability may be transferred to the component in the simulated population (Gentle, 1998). At each step, the goal is to achieve distribution values for the component that reflect not only known physiology or known direct observations, but also values that can be transformed

into a distribution that can be modeled and used in selecting random members to contribute to the final requirement distribution. When the final distribution representing the convolution of components has been derived, then the median and ninety-seventh and one-half percentile of the distribution can be directly estimated. It is recognized that, in its simplest form, the Monte Carlo approach ignores possible correlation among components. In the case of iron, however, expected correlation is built into the modeling of the requirement where components are linked to a common variable, such as growth rate, so that not all sources of correlation are neglected. These methods and their statistical basis are described in detail in the DRI report *Dietary Reference Intakes: Applications in Dietary Assessment* (IOM, 2000a).

Other Uses of the EAR

The EAR may also be used in the assessment of the intake of groups (IOM, 2000a) or, together with an estimate of the variance of intake, be used in planning for the intake of groups (IOM, 2003) (see Chapter 8).

Adequate Intake

If sufficient scientific evidence is not available to calculate an EAR, a reference intake called an *Adequate Intake* (AI) is provided instead of an RDA. The AI is a value based on experimentally derived intake levels or approximations of observed mean nutrient intakes by a group (or groups) of healthy people. The AIs for children and adults are expected to meet or exceed the amount needed to maintain a defined nutritional state or criterion of adequacy in essentially all members of a specific apparently healthy population. Examples of defined nutritional states include normal growth, maintenance of normal circulating nutrient values, or other aspects of nutritional well-being or general health.

As is the case in this report for determining the recommended intakes of water, potassium, sodium, and chloride, the AI is set when data are considered to be insufficient or inadequate to establish an EAR on which to base an RDA. For example, for young infants for whom human milk is the recommended sole source of food for almost all nutrients for the first 4 to 6 months, the AI is based on the daily mean nutrient intake supplied by human milk for healthy full-term infants who are exclusively fed human milk. For adults, the AI may be based on data from a single experiment, on esti-

mated dietary intakes in apparently healthy population groups, or on a review of data from different approaches that considered alone do not permit a reasonably confident estimate of an EAR.

Similarities Between the AI and the RDA

Both the AI and RDA are to be used as a goal for individual intake and thus both represent recommended levels of intake for individuals. In general, the values are intended to cover the needs of nearly all persons in a life stage group. (For infants, the AI is the mean intake when infants in the age group are consuming human milk. Larger infants may have greater needs, which they meet by consuming more milk.) As with RDAs, AIs for children and adolescents may be extrapolated from adult values if no other usable data are available.

Differences Between the AI and the RDA

There is much less certainty about the AI value than about the RDA value. Because AIs depend on a greater degree of judgment than is applied in estimating the EAR and subsequently the RDA, the AI may deviate significantly from and be numerically higher than the RDA. For this reason, AIs must be used with greater care than is the case for RDAs (see IOM, 2003). Also, the RDA is usually calculated from the EAR by using a formula that takes into account the expected variation in the requirement for the nutrient, which is not the case for some AIs (see previous section, "Estimated Average Requirement").

For some nutrients and food components, data are not sufficient for developing either an AI or an RDA for apparently healthy individuals. This is the case for sulfate (Chapter 7), as its requirement appears to be met by consumption of the sulfur-containing amino acids methionine and cysteine, and adequate data are lacking to determine the extent to which inclusion of sulfate in the diet can decrease the requirements for these indispensable amino acids.

Tolerable Upper Intake Level

The *Tolerable Upper Intake Level* (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all apparently healthy individuals in the specified life stage group (see Figure 1-1). As intake increases above the UL, the potential risk of adverse effects may increase. The term *tolerable in-*

take was chosen to avoid implying a possible beneficial effect. Instead, the term is intended to connote a level of intake that can, with high probability, be tolerated biologically. The UL is not intended to be a recommended level of intake, and there is no established benefit to healthy individuals if they consume a nutrient in amounts exceeding the recommended intake (the RDA or AI).

The UL is based on an evaluation conducted by using the methodology for risk assessment of nutrients (see Chapter 3). The need for setting ULs grew out of the increased fortification of foods with nutrients and the use of dietary supplements by more people and in larger doses. The UL applies to chronic daily use. As in the case of applying AIs, professionals should avoid very rigid application of ULs and first assess the characteristics of the individual and group of concern, such as the source of the nutrient, the physiological state of the individual, the length of sustained high intakes, and so forth.

For some nutrients, data are not sufficient for developing a UL for apparently healthy individuals. This indicates the need for caution in consuming amounts greater than the recommended intakes; it does not mean that high intakes pose no risk of adverse effects.

The safety of routine, long-term intake above the UL is not well documented. Although members of the general population should be advised not to routinely exceed the UL, intake above the UL may be appropriate for investigation within well-controlled clinical trials. Clinical trials of doses above the UL should not be discouraged as long as subjects participating in these trials have signed informed consent documents regarding possible toxicity and as long as these trials employ appropriate safe monitoring of trial subjects.

Determination of Adequacy

In the derivation of the AIs in this report, close attention has been paid to the determination of the most appropriate indicators of adequacy. A key question is: Adequate for what? In many cases, a continuum of benefits may be ascribed to various levels of intake of the same nutrient. One criterion may be deemed the most appropriate to determine the risk that an individual will become deficient in the nutrient whereas another criterion chosen may relate to reducing the risk of chronic degenerative disease, such as blood pressure in relation to hypertension.

In other reports providing DRIs for nutrients (IOM, 1997, 1998, 2000b, 2001, 2002/2005), as for those included in this report, each EAR or AI is described in terms of the selected criterion. The po-

tential role of the nutrient in the reduction of disease risk was considered in developing the EARs and AIs. With the acquisition of additional data relating intake to chronic disease or disability, the choice of the criteria used for setting these DRIs may change.

PARAMETERS FOR DIETARY REFERENCE INTAKES

Life Stage Groups

The life stage groups described below were chosen by keeping in mind all of the nutrients to be reviewed, not only those included in this report (see IOM, 1997). Additional subdivisions within these groups may be added in later reports. If data are too sparse to distinguish differences in requirements by life stage or gender group, the analysis may be presented for a larger grouping.

Infancy

Infancy covers the period from birth through 12 months of age and is divided into two 6-month intervals. The first 6-month interval was not subdivided further because intake is relatively constant during this time. That is, as infants grow, they ingest more food; however, on a body weight basis their intake remains the same. During the second 6 months of life, growth velocity slows, and thus total daily nutrient needs on a body weight basis may be less than those during the first 6 months of life.

For a particular nutrient, the average intake by full-term infants who are born to healthy, well-nourished mothers and exclusively fed human milk has been adopted as the primary basis for deriving the AI for nutrients during the first 6 months of life. The value used is thus not an EAR, and it is not assumed that such data will become available. The extent to which intake of human milk in the amounts recommended may result in exceeding the actual requirements of the infant is not known, and ethics of experimentation preclude testing levels known to be potentially inadequate.

Using the infant that is fed human milk as a model is in keeping with the basis for estimating nutrient allowances of infants as was developed in the last Recommended Dietary Allowances (RDA) (NRC, 1989) and Recommended Nutrient Intakes (RNI) (Health Canada, 1990) reports. It also supports the recommendation that exclusive human milk feeding is the preferred method of feeding for normal full-term infants for the first 4 to 6 months of life. This recommendation has also been made by the Canadian Paediatric

Society (Health Canada, 1990), by the American Academy of Pediatrics (AAP, 1997), and in the Food and Nutrition Board report *Nutrition During Lactation* (IOM, 1991).

In general, special consideration was not given to possible variations in physiological need during the first month after birth or to the variations in intake of nutrients from human milk that result from differences in milk volume and nutrient concentration during early lactation. Specific recommended intakes to meet the needs of formula-fed infants are not proposed in this report. The previously published RDAs and RNIs for infants have led to much misinterpretation of the adequacy of human milk because of a lack of understanding about their derivation for young infants. Although they were based on human milk composition and volume of intake, the previous RDA and RNI values allowed for lower bioavailability of nutrients from nonhuman milk.

Ages 0 Through 6 Months. To derive the AI value for infants ages 0 through 6 months, the mean intake of a nutrient was calculated on the basis of the average concentration of the nutrient from 2 through 6 months of lactation with use of consensus values for the nutrient from several reported studies (Atkinson et al., 1995), and an estimated average volume of milk intake of 0.78 L/day as reported from studies of full-term infants by test weighing, a procedure in which the infant is weighed before and after each feeding (Butte et al., 1984; Chandra, 1984; Hofvander et al., 1982; Neville et al., 1988). Because there is variation in both of these measures, the computed value represents the mean. It is expected that infants will consume increased volumes of human milk as they grow.

Ages 7 Through 12 Months. Except for some nutrients such as iron and zinc, for which infants have relatively high requirements, there is no evidence for markedly different nutrient needs during the period of infants' slower growth and gradual weaning to a mixed diet of human milk and solid foods from ages 7 through 12 months. The basis of the AI values derived for this age category was the sum of the specific nutrient provided by 0.6 L/day of human milk, which is the average volume of milk reported from studies in this age category (Heinig et al., 1993), and those provided by the usual intakes of complementary weaning foods consumed by infants of this age (Specker et al., 1997). This approach is in keeping with the current recommendations of the Canadian Paediatric Society (Health Canada, 1990), the American Academy of Pediatrics (AAP, 1997), and *Nutrition During Lactation* (IOM,

1991) for continued feeding of human milk to infants through 9 to 12 months of age with appropriate introduction of solid foods.

One problem that occurs in estimating intake data in infants is the lack of available data on total nutrient intake from a combination of human milk and solid foods in the second 6 months of life. Most intake survey data do not identify the milk source, but the published values for total intake indicate that cow milk or formula based on cow milk was most likely consumed along with weaning foods (Specker et al., 1997).

Toddlers: Ages 1 Through 3 Years

The greater velocity of growth in height during ages 1 through 3 years compared with ages 4 through 5 years provides a biological basis for dividing this period of life. Because children in the United States and Canada from age 4 years onwards begin to enter the public school system, ending this life stage prior to age 4 years seemed appropriate. Data are sparse for indicators of nutrient adequacy on which to derive DRIs for these early years of life. In some cases, DRIs for this age group were derived from data extrapolated from studies of infants or of adults ages 19 years and older.

Early Childhood: Ages 4 Through 8 Years

Because major biological changes in velocity of growth and changing endocrine status occur during ages 4 through 8 or 9 years (the latter depending on onset of puberty in each gender), the category of 4 through 8 years is appropriate. For many nutrients, but not those covered in this report, a reasonable amount of data is available on nutrient intake and various criteria for adequacy (such as nutrient balance measured in young children aged 5 through 7 years) that can be used as the basis for the EARs and AIs for this life stage group.

Puberty/Adolescence: Ages 9 Through 13 Years and 14 Through 18 Years

Because current data support younger ages for pubertal development, it was determined that the adolescent age group should begin at 9 years. The mean age of onset of breast development (Tanner Stage 2) for white girls in the United States is 10.0 ± 1.8 (standard deviation) years; this is a physical marker for the beginning of increased estrogen secretion (Herman-Giddens et al., 1997).

In African-American girls, onset of breast development is earlier (mean 8.9 years ± 1.9). The reason for the observed racial differences in the age at which girls enter puberty is unknown. The onset of the growth spurt in girls begins before the onset of breast development (Tanner, 1990). The age group of 9 through 13 years allows for this early growth spurt of females.

For boys, the mean age of initiation of testicular development is 10.5 to 11 years, and their growth spurt begins 2 years later (Tanner, 1990). Thus, to begin the second age category at 14 years and to have different EARs and AIs for girls and boys for some nutrients at this age seems biologically appropriate. All children continue to grow to some extent until as late as age 20 years; therefore, having these two age categories span the period 9 through 18 years of age seems justified.

Young Adulthood and Middle Ages: Ages 19 Through 30 Years and 31 Through 50 Years

The recognition of the possible value of higher nutrient intakes during early adulthood on achieving optimal genetic potential for peak bone mass was the reason for dividing adulthood into ages 19 through 30 years and 31 through 50 years. Moreover, mean energy expenditure decreases from 19 through 50 years, and needs for nutrients related to energy metabolism may also decrease. For some nutrients, such as sodium and potassium in this report, the DRIs may be the same for the two age groups. However, for other nutrients, especially those related to energy metabolism, EARs (and thus RDAs) and AIs are likely to differ for these two age groups.

Adulthood and Older Adults: Ages 51 Through 70 Years and Over 70 Years

The age period of 51 through 70 years spans active work years for most adults. After age 70 years, people of the same age increasingly display variability in physiological functioning and physical activity. A comparison of people over age 70 years who are the same chronological age may demonstrate as much as a 15- to 20-year age-related difference in level of reserve capacity and functioning. This is demonstrated by age-related declines in nutrient absorption and renal function. Because of the high variability in functional capacity of older adults, the EARs and AIs for this age group may reflect a greater variability in requirements for the older age categories. This

variability may be most applicable to nutrients for which requirements are related to energy expenditure.

Pregnancy and Lactation

Recommendations for pregnancy and lactation may be subdivided because of the many physiological changes and changes in nutrient needs that occur during these life stages. In setting EARs and AIs for these life stages, however, consideration is given to adaptations to increased nutrient demand, such as increased absorption and greater conservation of many nutrients. Moreover, nutrients may undergo net losses due to physiological mechanisms regardless of the nutrient intake such as seen with calcium in lactation (IOM, 1997). Thus, for some nutrients, there may not be a basis for EAR or AI values that are different during these life stages than they are for other women of comparable age.

Reference Heights and Weights

Use of Reference Heights and Weights

Reference heights and weights are useful when more specificity about body size and nutrient requirements are needed than that provided by life stage categories. For example, while the EAR may be developed for the 4- to 8-year-old age group, a small 4-year-old child may be assumed to require less than the EAR for that age group, whereas a large 8-year-old may require more than the EAR. Based on the model for establishing RDAs, however, the RDA (and an AI) should meet the needs of both.

In some cases, where data regarding nutrient requirements are reported on a body-weight basis, it is necessary to have reference heights and weights to transform the data for comparison purposes. Frequently, where data regarding adult requirements represent the only available data (e.g., on adverse effects of chronic high intakes for establishing Tolerable Upper Intake Levels [ULs]), extrapolating on the basis of body weight or size becomes a possible option to providing ULs for other age groups. Thus, for this and other reports, when data are not available, the EAR or UL for children or for pregnant women may be established by extrapolation from adult values on the basis of body weight. It should be noted that, depending on the nutrient, the value may also be extrapolated based on relative energy expenditure.

New Reference Heights and Weights

As is described in Appendix B, the DRI framework is an iterative process that was initiated in 1994. Thus reference heights and weights used in some of the earlier DRI reports for the U.S. and Canadian populations (IOM, 1997, 1998, 2000b, 2001) were developed based on data from the Third National Health and Nutrition Examination Survey on body mass index (BMI) for children and young adults (IOM, 1997). With the recent publication of new U.S.-based growth charts for infants and children and the introduction of BMI recommendations for adults (Kuczmarski et al., 2000), reference heights and weights for adults and children have been updated and are now used in more recent DRI reports (IOM, 2002/2005). Besides being more current, these new reference heights and weights are more representative of the U.S. and Canadian populations. Table 1-1 provides these updated values. Appendix B includes information about the reference values that were used in the earlier DRI reports.

TABLE 1-1 Current Reference Heights and Weights for Children and Adults in the United States

Sex	Age	Median Body Mass Index[a] (kg/m^2)	Median Reference Height[a] cm (in)	Reference Weight[b] kg (lb)
Male, female	2–6 mo	—	62 (24)	6 (13)
	7–12 mo	—	71 (28)	9 (20)
	1–3 y	—	86 (34)	12 (27)
	4–8 y	15.3	115 (45)	20 (44)
Male	9–13 y	17.2	144 (57)	36 (79)
	14–18 y	20.5	174 (68)	61 (134)
	19–30 y	22.5	177 (70)	70 (154)
Female	9–13 y	17.4	144 (57)	37 (81)
	14–18 y	20.4	163 (64)	54 (119)
	19–30 y	21.5	163 (64)	57 (126)

[a] Taken from data on male and female median body mass index and height-for-age data from the Centers for Disease Control and Prevention (CDC)/National Center for Health Statistics (NCHS) Growth Charts (Kuczmarski et al., 2000).

[b] Calculated from CDC/NCHS Growth Charts (Kuczmarski et al., 2000); median body mass index and median height for ages 4 through 19 years.

SUMMARY

Dietary Reference Intakes (DRIs) is a generic term for a set of nutrient reference values that includes the Estimated Average Requirement, the Recommended Dietary Allowance, the Adequate Intake, and the Tolerable Upper Intake Level. These reference values are being developed for specific life stage and gender groups in a joint U.S. and Canadian activity. This report—one volume in a series—covers the DRIs for water and the electrolytes potassium, sodium, chloride, and sulfate.

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2
Overview and Methods

SUMMARY

The general methods for examining and interpreting the evidence on requirements for nutrients are presented in this chapter, with special attention given to approaches used to provide Dietary Reference Intakes (DRIs) where data are lacking for specific subgroups of the population (typically for infants, children, pregnant and lactating women, and older adults). Included as well are discussions of methodological problems in assessing requirements and estimating intakes from dietary survey data. Relevant detail is provided in the nutrient chapters that follow.

BACKGROUND

This report focuses on water, potassium, sodium, chloride, and sulfate. Those that provide a specific beneficial role in human physiological processes and health include water, potassium, sodium, and chloride. Sulfate, while essential for specific metabolic functions, can be formed in sufficient quantities from adequate intakes of sulfur-containing amino acids. Water is the largest single constituent of the human body and is essential for cellular homeostasis and life. Water provides the solvent for biochemical reactions, is the medium for material transport, has unique physical properties (e.g., high specific heat) to absorb metabolic heat, and is essential to maintain blood volume to support cardiovascular function and renal filtration. Potassium is the major intracellular cation and is re-

quired for normal cellular function. Severe potassium deficiency is characterized by hypokalemia, and its adverse consequences include cardiac arrhythmias, muscle weakness, and insulin resistance. More subtle deficiency signs of potassium are increased blood pressure, increased sensitivity of blood pressure to sodium intake ("salt sensitivity"), increased risk of kidney stones, and increased bone turnover. Sodium chloride is required to maintain fluid and electrolyte balance, extracellular volume, and serum osmolality.

METHODOLOGICAL CONSIDERATIONS

Types of Data Used

The scientific data for developing the Dietary Reference Intakes (DRIs) have essentially come from observational and experimental studies in humans. Observational studies include single-case and case-series reports and cross-sectional, cohort, and case-control studies. Experimental studies include randomized and nonrandomized prevention trials and controlled dose-response, balance, turnover, and depletion-repletion physiological studies. Results from animal experiments are generally not applicable to the establishment of DRIs, but selected animal studies are considered in the absence of human data.

Animal Models

Basic research using experimental animals affords considerable advantage in terms of control of nutrient exposures, environmental factors, and even genetics. In contrast, the relevance to free-living humans may be unclear. In addition, dose levels and routes of administration that are practical in animal experiments may differ greatly from those relevant to humans. Nevertheless, animal feeding experiments were sometimes included in the evidence reviewed to determine the ability to specify DRIs.

Human Feeding Studies

Controlled feeding studies, usually in a confined setting such as a metabolic unit, can yield valuable information on the relationship between nutrient consumption and health-related biomarkers. Much of the understanding of human nutrient requirements to prevent deficiencies is based on studies of this type. Studies in which the subjects are confined allow for close control of both in-

take and activities. Complete collections of nutrient losses through urine and feces are possible, as are recurring sampling of biological materials such as blood. Nutrient balance studies measure nutrient status in relation to intake. Depletion-repletion studies, by contrast, measure nutrient status while subjects are maintained on diets containing marginally low or deficient levels of a nutrient; then the deficit is corrected with measured amounts of that nutrient. Unfortunately, these two types of studies have several limitations. Typically they are limited in time to a few days or weeks, and so longer-term outcomes cannot be measured with the same level of accuracy. In addition, subjects may be confined, and findings are therefore not always generalizable to free-living individuals. Finally, the time and expense involved in such studies usually limit the number of subjects and the number of doses or intake levels that can be tested.

In spite of these limitations, feeding studies play an important role in understanding nutrient needs and metabolism. Such data were considered in the DRI process and were given particular attention in the absence of reliable data to directly relate nutrient intake to disease risk.

Observational Studies

In comparison to human feeding studies, observational epidemiological studies are frequently of direct relevance to free-living humans, but they lack the controlled setting. Hence they are useful in establishing evidence of an association between the consumption of a nutrient and disease risk but are limited in their ability to ascribe a causal relationship. A judgment of causality may be supported by a consistency of association among studies in diverse populations, and it may be strengthened by the use of laboratory-based tools to measure exposures and confounding factors, such as personal interviews, rather than other means of data collection. In recent years, rapid advances in laboratory technology have made possible the increased use of biomarkers of exposure, susceptibility, and disease outcome in molecular epidemiological research. For example, one area of great potential in advancing current knowledge of the effects of diet on health is the study of genetic markers of disease susceptibility (especially polymorphisms in genes encoding metabolizing enzymes) in relation to dietary exposures. This development is expected to provide more accurate assessments of the risk associated with different levels of intake of both nutrients and nonnutritive food constituents.

While analytic epidemiological studies (studies that relate exposure to disease outcomes in individuals) have provided convincing evidence of an associative relationship between selected nondietary exposures and disease risk, there are a number of other factors that limit study reliability in research relating nutrient intakes to disease risk.

First, the variation in nutrient intake may be rather limited in populations selected for study. This feature alone may yield modest relative risk trends across intake categories in the population, even if the nutrient is an important factor in explaining large disease rate variations among populations.

A second factor, one that gives rise to particular concerns about confounding, is the human diet's complex mixture of foods and nutrients that includes many substances that may be highly correlated. Third, many cohort and case-control studies have relied on self-reports of diet, typically food records, 24-hour recalls, or diet history questionnaires. Repeated application of such instruments to the same individuals shows considerable variation in nutrient consumption estimates from one time period to another with correlations often in the 0.3 to 0.7 range (e.g., Willett et al., 1985). In addition, there may be systematic bias in nutrient consumption estimates from self-reports as the reporting of food intakes and portion sizes may depend on individual characteristics such as body mass, ethnicity, and age. For example, total energy consumption may tend to be substantially underreported (30 to 50 percent) among obese persons, with little or no underreporting among lean persons (Heitmann and Lissner, 1995). Such systematic bias, in conjunction with random measurement error and limited intake range, has the potential to greatly impact analytic epidemiological studies based on self-reported dietary habits. Note that cohort studies using objective (biomarker) measures of nutrient intake may have an important advantage in the avoidance of systematic bias, though important sources of bias (e.g., confounding) may remain.

Randomized Clinical Trials

By randomly allocating subjects to the (nutrient) exposure of interest, clinical trials eliminate the confounding that may be introduced in observational studies by self-selection. The unique strength of randomized trials is that, if the sample is large enough, the study groups will be similar with respect not only to those confounding variables known to the investigators, but also to any unknown factors that might be related to risk of the disease. Thus, randomized

trials achieve a degree of control of confounding that is simply not possible with any observational design strategy, and thus they allow for the testing of small effects that are beyond the ability of observational studies to detect reliably.

Although randomized controlled trials represent the accepted standard for studies of nutrient consumption in relation to human health, they too possess important limitations. Specifically, persons agreeing to be part of a randomized trial may be a select subset of the population of interest, thus limiting the generalization of trial results. For practical reasons, only a small number of nutrients or nutrient combinations at a single intake level are generally studied in a randomized trial (although a few intervention trials to compare specific dietary patterns have been initiated in recent years). In addition, the follow-up period will typically be short relative to the preceding time period of nutrient consumption that may be relevant to the health outcomes under study, particularly if chronic disease endpoints are sought. Also, dietary intervention or supplementation trials tend to be costly and logistically difficult, and the maintenance of intervention adherence can be a particular challenge.

Because of the many complexities in conducting studies among free-living human populations and the attendant potential for bias and confounding, it is the totality of the evidence from both observational and intervention studies, appropriately weighted, that must form the basis for conclusions about causal relationships between particular exposures and disease outcomes.

Weighing the Evidence

As a principle, only studies published in peer-reviewed journals have been used in this report. However, studies published in other scientific journals or readily available reports were considered if they appeared to provide important information not documented elsewhere. To the extent possible, original scientific studies have been used to derive the DRIs. On the basis of a thorough review of the scientific literature, clinical, functional, and biochemical indicators of nutritional adequacy and excess were evaluated for each nutrient.

The quality of the study was considered in weighing the evidence. The characteristics examined included the study design and the representativeness of the study population; the validity, reliability, and precision of the methods used for measuring intake and indicators of adequacy or excess; the control of biases and confounding

factors; and the power of the study to demonstrate a given difference or correlation. Publications solely expressing opinions were not used in setting DRIs. The assessment acknowledged the inherent reliability of each type of study design as described above, and it applied standard criteria concerning the strength, dose-response, and temporal pattern of estimated nutrient-disease or adverse effect associations, the consistency of associations among studies of various types, and the specificity and biological plausibility of the suggested relationships (Hill, 1971). For example, biological plausibility would not be sufficient in the presence of a weak association and lack of evidence that exposure preceded the effect.

Data were examined to determine whether similar estimates of the requirement resulted from the use of different indicators and different types of studies. In the DRI model described in Chapter 1, for a single nutrient, the criterion for setting the Estimated Average Requirement (EAR) may differ from one life stage group to another because the critical function or the risk of disease may be different. When no or very poor data are available for a given life stage group, extrapolation is made from the EAR or Adequate Intake (AI) set for another group (see later section on extrapolation); explicit and logical assumptions on relative requirements were made. Because EARs can be used for multiple purposes, unlike AIs, they are established whenever sufficient supporting data were available.

Data Limitations

Although the reference values in these DRI reports are based on data, the data were often scanty or drawn from studies that had limitations in addressing the various questions that confronted the panel. Therefore, many of the questions raised about the requirements for and recommended intakes of these nutrients cannot be answered fully because of inadequacies in the present database. Apart from studies of overt deficiency diseases, there is a dearth of studies that address specific effects of inadequate intakes on specific indicators of health status, and thus a research agenda is proposed (see Chapter 9). For many of the nutrients in the DRI reports, estimated requirements are based on factorial, balance, and biochemical indicator data because there is little information relating health status indicators to functional sufficiency or insufficiency.

Thus, after careful review and analysis of the evidence, including examination of the extent of congruent findings, scientific judg-

ment was used to determine the basis for establishing the values. The reasoning used is described for each nutrient in Chapters 4 through 7.

Method for Determining the Adequate Intake for Infants

The AI for young infants is generally taken to be the average intake by full-term infants who are born to healthy, well-nourished mothers and who are exclusively fed human milk. The extent to which intake of a nutrient from human milk may exceed the actual requirements of infants is not known, and ethics of experimentation preclude testing the levels known to be potentially inadequate. Using the infant exclusively fed human milk as a model is in keeping with the basis for earlier recommendations for intake (e.g., Health Canada, 1990; IOM, 1991). It also supports the recommendation that exclusive intake of human milk is the preferred method of feeding for normal full-term infants for the first 4 to 6 months of life. This recommendation has been made by the Canadian Paediatric Society (Health Canada, 1990), the American Academy of Pediatrics (AAP, 1997), the Institute of Medicine (IOM, 1991), and many other expert groups, even though most U.S. babies no longer receive human milk by age 6 months.

In general, this report does not cover possible variations in physiological need during the first month after birth or the variations in intake of nutrients from human milk that result from differences in milk volume and nutrient concentration during early lactation.

In keeping with the decision made by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, specific recommended intakes to meet the needs of formula-fed infants have not been proposed in this report. The use of formula introduces a large number of complex issues, one of which is the bioavailability of different forms of the nutrient in different formula types.

Ages 0 Through 6 Months

To derive the AI for infants ages 0 through 6 months, the mean intake of a nutrient was calculated based on (1) the average concentration of the nutrient from 2 to 6 months of lactation using consensus values from several reported studies, if possible, and (2) an average volume of milk intake of 0.78 L/day. This volume was reported from studies that used test weighing of full-term infants. In this procedure, the infant is weighed before and after each feeding (Butte et al., 1984; Chandra, 1984; Hofvander et al., 1982;

Neville et al., 1988). Because there is variation in both the composition of milk and the volume consumed, the computed value represents the mean. It is expected that infants will consume increased volumes of human milk during growth spurts.

Ages 7 Through 12 Months

During the period of infant growth and gradual weaning to a mixed diet of human milk and solid foods from ages 7 through 12 months, there is no evidence for markedly different nutrient needs. The AI can be derived for this age group by calculating the sum of (1) the content of the nutrient provided by 0.6 L/day of human milk, which is the average volume of milk reported from studies of infants receiving human milk in this age category (Heinig et al., 1993) and (2) that provided by the usual intakes of complementary weaning foods consumed by infants in this age category. Such an approach is in keeping with the current recommendations of the Canadian Paediatric Society (Health Canada, 1990), the American Academy of Pediatrics (AAP, 1997), and the Institute of Medicine (IOM, 1991) for continued feeding of infants with human milk through 9 to 12 months of age with appropriate introduction of solid foods. The World Health Organization recommends the introduction of solid foods after 6 months of age (WHO, 2002). In this report the amounts of potassium and sodium from complementary foods were estimated National Health and Nutrition Examination Survey (NHANES) III data and are presented in the nutrient chapters.

For some of the nutrients in other DRI reports, two other approaches were considered as well: (1) extrapolation downward from the EAR for young adults by adjusting for metabolic or total body size and growth and adding a factor for variability and (2) extrapolation upward from the AI for infants ages 0 through 6 months by using the same type of adjustment. Both of these methods are described below. The results of the methods are evaluated in the process of setting the AI.

Method for Extrapolating Data from Younger to Older Infants

When information is not available on the nutrient intake of older infants, intake data can be extrapolated from young to older infants. Using the metabolic weight ratio method to extrapolate data from younger to older infants involves metabolic scaling but does not include an adjustment for growth because it is based on a value

for a growing infant. To extrapolate from the AI for infants ages 0 through 6 months to an AI for infants ages 7 through 12 months, the following formula is used:

$$AI_{7–12\ mo} = AI_{0–6\ mo} \times F,$$

where $F = (Weight_{7–12\ mo}/Weight_{0–6\ mo})^{0.75}$.

Method for Extrapolating Data from Adults to Infants and Children

Setting the AI for Children

For water, potassium, and sodium, data were not available to set the EAR and Recommended Dietary Allowance (RDA) for children ages 1 year and older and for adolescents. In the case of sodium and potassium, the AI was extrapolated down from adults by using the average of median energy intakes for both genders for each age group from NHANES II data (IOM, 2002/2005). Extrapolating on the basis of energy intake was used rather than on the basis of body weight because high levels of physical activity have an effect on losses of electrolytes in sweat.

The formula for the extrapolation is

$$AI_{child} = AI_{adult} \times F,$$

where $F = (\text{Energy Intake}_{child}/\text{Energy Intake}_{adult})$.

Setting the Tolerable Upper Intake Level for Children

Because data were not available to set the Tolerable Upper Intake Level (UL) for sodium for children, the UL for adults was extrapolated down using the median energy intakes (kcal/day for each age group) (IOM, 2002/2005):

$$UL_{child} = UL_{adult} \times \text{Energy Intake}_{adult}/\text{Energy Intake}_{child}.$$

Energy intake was used as the basis for extrapolation rather than body weight because this method was not used in the nutrients included in the report.

Method for Extrapolating Data from Younger Adults to Older Adults

For sodium the AI for older adults is extrapolated from younger adults based on the combined average of median energy intakes for

men and women. Median energy intakes ranged from 1,507 to 2,109 kcal/day for men and women (51–70 years) to 1,356 to 1,978 kcal/day (> 70 years) based on NHANES III data (IOM, 2002/2005). The average of these ranges was used to extrapolate from younger adults who consumed more energy than older adults. However, for potassium the intake was not adjusted down for older adults because of the increased risk of elevated blood pressure with aging.

Methods for Determining Increased Needs for Pregnancy

It is known that the placenta actively transports certain nutrients from the mother to the fetus against a concentration gradient (Hytten and Leitch, 1971). However, for many nutrients, including sodium and potassium, experimental data that could be used to set an EAR and RDA or an AI for pregnancy are lacking. In these cases, the potential increased need for these nutrients during pregnancy is based on theoretical considerations, including obligatory fetal transfer, if data are available, and on increased maternal needs related to increases in energy or protein metabolism, as applicable. Because there was insufficient evidence to suggest that an AI for potassium or sodium during pregnancy should be quantitatively different from that of nonpregnant women and because pregnant women consumed within the energy range of nonpregnant women, an AI was not set differently for pregnant women.

Methods for Determining Increased Needs for Lactation

It is assumed that the total nutrient requirement for sodium, potassium, and water for lactating women equals the requirement for nonpregnant, nonlactating women of similar age plus an increment to cover the amount needed for milk production. Details are provided in each nutrient chapter.

ESTIMATES OF NUTRIENT INTAKE

Reliable and valid methods of food composition analysis are crucial in determining the intake of a nutrient needed to meet a requirement. For nutrients such as sodium, estimating intake has been challenging because of the difficulty in assessing the amount of sodium chloride (salt) added to foods during cooking and during eating.

Methodological Considerations

The quality of nutrient intake data varies widely across studies. The most valid intake data are those collected from the metabolic study protocols in which all food is provided by the researchers, amounts consumed are measured accurately, and the nutrient composition of the food is determined by reliable and valid laboratory analyses. Such protocols are usually possible with only a few subjects. Thus, in many studies, intake data are self-reported (e.g., through 24-hour recalls of food intake, diet records, or food frequency questionnaires).

Potential sources of error in self-reported intake data include over- or underreporting of portion sizes and frequency of intake, omission of foods, and inaccuracies related to the use of food composition tables (IOM, 2000; Lichtman et al., 1992; Mertz et al., 1991). In addition, because a high percentage of the food consumed in the United States and Canada is not prepared from scratch in the home, errors can occur due to a lack of information on how a food was manufactured, prepared, and served. Therefore, the values reported by nationwide surveys or studies that rely on self-report are often inaccurate and possibly biased, with a greater tendency to underestimate actual intake (IOM, 2000).

Because of day-to-day variation in dietary intakes, the distribution of 1-day (or 2-day) intakes for a group is wider than the distribution of usual intakes even though the mean of the intakes may be the same. To reduce this problem, statistical adjustments have been developed (NRC, 1986; Nusser et al., 1996) that require at least 2 days of dietary data from a representative subsample of the population of interest. However, no accepted method is available to adjust for the underreporting of intake, which may average as much as 20 percent for energy (Mertz et al., 1991).

DIETARY INTAKES IN THE UNITED STATES AND CANADA

Sources of Dietary Intake Data

The major sources of current dietary intake data for the U.S. population are the Third National Health and Nutrition Examination Survey (NHANES III), which was conducted from 1988 to 1994 by the U.S. Department of Health and Human Services, and the Continuing Survey of Food Intakes by Individuals (CSFII), which was conducted by the U.S. Department of Agriculture (USDA) from

1994 to 1996. NHANES III examined 30,000 subjects aged 2 months and older. A single 24-hour diet recall was collected for all subjects. A second recall was collected for a 5 percent nonrandom subsample to allow adjustment of intake estimates for day-to-day variation. NHANES III also collected various biochemical data on a subset of subjects. The 1994 to 1996 CSFII collected two nonconsecutive 24-hour recalls from approximately 16,000 subjects of all ages. Both surveys used the food composition database developed by USDA to calculate nutrient intakes (Perloff et al., 1990) and were adjusted by the method of Nusser et al. (1996). National survey data for Canada for these nutrients have been collected in 10 provinces.

Appendixes D and E provide the mean and the fifth through ninety-ninth percentiles of dietary intakes of sodium, potassium, and water from NHANES III and CFSII, adjusted by methods described by the National Research Council (NRC, 1986) and by Feinleib and coworkers (1993) and adjusted for day-to-day variation by the method of Nusser and coworkers (1996). Appendix F provides means and selected percentiles of dietary intakes for adults in 10 provinces.

Food Sources

For some nutrients, two types of information are provided about food sources: identification of the foods that are the major contributors of the nutrients to diets in the United States and Canada and identification of the foods that contain the highest amounts of the nutrient. The determination of foods that are major contributors depends on both nutrient content of a food and the total consumption of the food (amount and frequency). Therefore, a food that has a relatively low concentration of the nutrient might still be a large contributor to total intake if that food is consumed in relatively large amounts.

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3

A Model for the Development of Tolerable Upper Intake Levels

BACKGROUND

The Tolerable Upper Intake Level (UL) refers to the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects increases. The term *tolerable* is chosen because it connotes a level of intake that can, with high probability, be tolerated biologically by individuals; it does not imply acceptability of that level in any other sense. The setting of a UL does not indicate that nutrient intakes greater than the Recommended Dietary Allowance (RDA) or Adequate Intake (AI) are recommended as being beneficial to an individual.[1] The UL is not meant to apply to individuals who are treated with the nutrient under medical supervision or to individuals with predisposing conditions that modify their sensitivity to the nutrient. This chapter describes a model for developing ULs.

The term *adverse effect* is defined as any significant alteration in the structure or function of the human organism (Klaassen et al., 1986) or any impairment of a physiologically important function that could lead to a health effect that is adverse, in accordance with the definition set by the joint World Health Organization (WHO),

[1] Many individuals are self-medicating with nutrients for curative or treatment purposes. It is beyond the scope of this report to address the possible therapeutic benefits of higher nutrient intakes that may offset the risk of adverse effects.

Food and Agriculture Organization of the United Nations (FAO), and International Atomic Energy Agency Expert Consultation in Trace Elements in Human Nutrition and Health (WHO, 1996). In the case of nutrients, it is exceedingly important to consider the possibility that the intake of one nutrient may alter, in detrimental ways, the health benefits conferred by another nutrient. Any such alteration (referred to as an adverse nutrient-nutrient interaction) is considered an adverse health effect. When evidence for such adverse interactions is available, it is considered in establishing a nutrient's UL.

ULs are useful because of the increased interest in and availability of fortified foods, the increased use of dietary supplements, and the growing recognition of the health consequences of excesses, as well as inadequacies, of nutrient intakes. ULs are based on total intake of a nutrient from food, water, and supplements if adverse effects have been associated with total intake. However, if adverse effects have been associated with intake from supplements or food fortificants only, the UL is based on a nutrient intake from those sources only, not on total intake. The UL applies to chronic daily use.

For many nutrients, there are insufficient data on which to develop a UL. This does not mean that there is no potential for adverse effects resulting from high intake. When data about adverse effects are extremely limited, extra caution may be warranted.

Like all chemical agents, nutrients can produce adverse health effects if their intake from a combination of food, water, nutrient supplements, and pharmacological agents is excessive. Some lower level of nutrient intake will ordinarily pose no likelihood (or risk) of adverse health effects in normal individuals even if the level is above that associated with any benefit. It is not possible to identify a single risk-free intake level for a nutrient that can be applied with certainty to all members of a population. However, it is possible to develop intake levels that are unlikely to pose risks of adverse health effects for most members of the general healthy population, including sensitive individuals. For some nutrients, these intake levels may pose a risk to subpopulations with extreme or distinct vulnerabilities.

It is not well documented whether routine, long-term intake above the UL is safe. Although members of the general population should not routinely exceed the UL, intake above the UL may be appropriate for investigation within well-controlled clinical trials. Clinical trials of doses above the UL should not be discouraged, as long as subjects participating in these trials have signed informed consent

documents regarding possible toxicity and as long as these trials employ appropriate safety monitoring of trial subjects.

A MODEL FOR THE DERIVATION OF TOLERABLE UPPER INTAKE LEVELS

The possibility that the methodology used to derive Tolerable Upper Intake Levels (ULs) might be reduced to a mathematical model that could be generically applied to all nutrients was considered. Such a model might have several potential advantages, including ease of application and assurance of consistent treatment of all nutrients. It was concluded, however, that the current state of scientific understanding of toxic phenomena in general, and nutrient toxicity in particular, is insufficient to support the development of such a model. Scientific information about various adverse effects and their relationships to intake levels varies greatly among nutrients and depends on the nature, comprehensiveness, and quality of available data. The uncertainties associated with the unavoidable problem of extrapolating, from the circumstances under which data are developed (e.g., in the laboratory or clinic) to other circumstances (e.g., the healthy population), adds to the complexity.

Given the current state of knowledge, any attempt to capture in a mathematical model all of the information and scientific judgments that must be made to reach conclusions about ULs would not be consistent with contemporary risk assessment practices. Instead, the model for the derivation of ULs consists of a set of scientific factors that always should be considered explicitly. The framework by which these factors are organized is called *risk assessment.* Risk assessment (NRC, 1983, 1994) is a systematic means of evaluating the probability of occurrence of adverse health effects in humans from excess exposure to an environmental agent (in this case, a nutrient) (FAO/WHO, 1995; Health Canada, 1993). The hallmark of risk assessment is the requirement to be explicit in all of the evaluations and judgments that must be made to document conclusions.

RISK ASSESSMENT AND FOOD SAFETY

Basic Concepts

Risk assessment is a scientific undertaking having as its objective a characterization of the nature and likelihood of harm resulting from human exposure to agents in the environment. The characteriza-

tion of risk typically contains both qualitative and quantitative information and includes a discussion of the scientific uncertainties in that information. In the present context, the agents of interest are nutrients, and the environmental media are food, water, and nonfood sources such as nutrient supplements and pharmacological preparations.

Performing a risk assessment results in a characterization of the relationships between exposure to an agent and the likelihood that adverse health effects will occur in members of exposed populations. Scientific uncertainties are an inherent part of the risk assessment process and are discussed below. Deciding whether the magnitude of exposure is *acceptable* or *tolerable* in specific circumstances is not a component of risk assessment; this activity falls within the domain of *risk management*. Risk management decisions depend on the results of risk assessments but may also involve the public health significance of the risk, the technical feasibility of achieving various degrees of risk control, and the economic and social costs of this control. Because there is no single scientifically definable distinction between safe and unsafe exposures, risk management necessarily incorporates components of sound, practical decision making that are not addressed by the risk assessment process (NRC, 1983, 1994).

Risk assessment requires that information be organized in rather specific ways but does not require any specific scientific evaluation methods. Rather, risk assessors must evaluate scientific information using what they judge to be appropriate methods and must make explicit the basis for their judgments, the uncertainties in risk estimates, and, when appropriate, alternative scientifically plausible interpretations of the available data (NRC, 1994; OTA, 1993).

Risk assessment is subject to two types of scientific uncertainties: those related to data and those associated with inferences that are required when directly applicable data are not available (NRC, 1994). Data uncertainties arise during the evaluation of information obtained from the epidemiological and toxicological studies of nutrient intake levels that are the basis for risk assessments. Examples of inferences include the use of data from experimental animals to estimate responses in humans and the selection of uncertainty factors to estimate inter- and intraspecies variabilities in response to toxic substances. Uncertainties arise whenever estimates of adverse health effects in humans are based on extrapolations of data obtained under dissimilar conditions (e.g., from experimental animal studies). Options for dealing with uncertainties are discussed below and in detail in Appendix K.

Steps in the Risk Assessment Process

The organization of risk assessment is based on a model proposed by the National Research Council (NRC, 1983, 1994) that is widely used in public health and regulatory decision making. The steps of risk assessment as applied to nutrients follow (see also Figure 3-1).

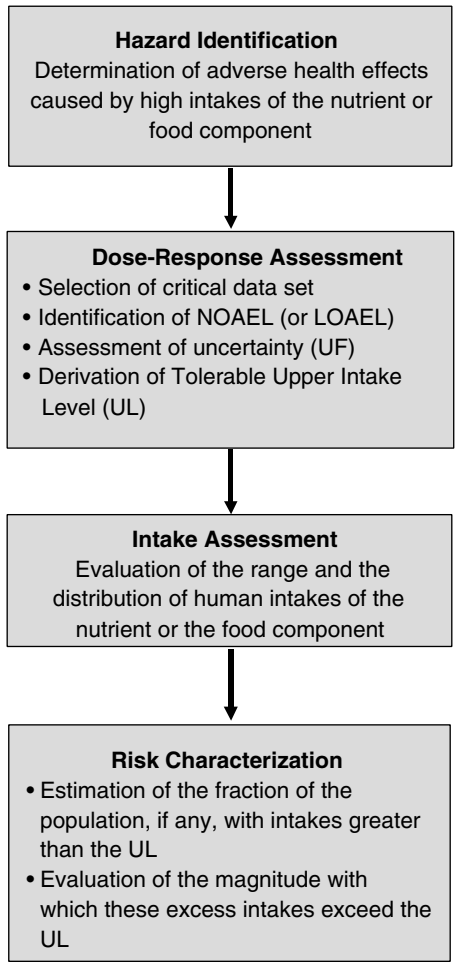

FIGURE 3-1 Risk assessment model for nutrient toxicity.

- Step 1. Hazard identification involves the collection, organization, and evaluation of all information pertaining to the adverse effects of a given nutrient. It concludes with a summary of the evidence concerning the capacity of the nutrient to cause one or more types of toxicity in humans.
- Step 2. Dose-response assessment determines the relationship between nutrient intake (dose) and adverse effect (in terms of incidence and severity). This step concludes with an estimate of the Tolerable Upper Intake Level (UL)—it identifies the highest level of daily nutrient intake that is likely to pose no risks of adverse health effects for almost all individuals in the general population. Different ULs may be developed for various life stage groups.
- Step 3. Intake assessment evaluates the distribution of usual total daily nutrient intakes for members of the general population. In cases where the UL pertains only to supplement use and does not pertain to usual food intakes of the nutrient, the assessment is directed at supplement intakes only. Step 3 does not depend on Step 1 or 2.
- Step 4. Risk characterization summarizes the conclusions from Steps 1 and 2 with Step 3 to determine the risk. The risk is generally expressed as the fraction of the exposed population, if any, having nutrient intakes (Step 3) in excess of the estimated UL (Steps 1 and 2). If possible, characterization also covers the magnitude of any such excesses. Scientific uncertainties associated with both the UL and the intake estimates are described so that risk managers understand the degree of scientific confidence they can place in the risk assessment.

The risk assessment contains no discussion of recommendations for reducing risk; these are the focus of risk management.

Thresholds

A principal feature of the risk assessment process for noncarcinogens is the long-standing acceptance that no risk of adverse effects is expected unless a threshold dose (or intake) is exceeded. The adverse effects that may be caused by a nutrient almost certainly occur only when the threshold dose is exceeded (NRC, 1994; WHO, 1996). The critical issues concern the methods used to identify the approximate threshold of toxicity for a large and diverse human population. Because most nutrients are not considered to be carcinogenic in humans, approaches used for carcinogenic risk assessment are not discussed here.

Thresholds vary among members of the general population (NRC, 1994). For any given adverse effect, if the distribution of thresholds in the population could be quantitatively identified, it would be possible to establish ULs by defining some point in the lower tail of the distribution of thresholds that would protect some specified fraction of the population. The method for identifying thresholds for a general population described here is designed to ensure that almost all members of the population will be protected, but it is not based on an analysis of the theoretical (but practically unattainable) distribution of thresholds. By using the model to derive the threshold, however, there is considerable confidence that the threshold, which becomes the UL for nutrients or food components, lies very near the low end of the theoretical distribution and is the end representing the most sensitive members of the population. For some nutrients, there may be subpopulations that are not included in the general distribution because of extreme or distinct vulnerabilities to toxicity. Data relating to the effects observed in these groups are not used to derive ULs. Such distinct groups, whose conditions warrant medical supervision, may not be protected by the UL.

The Joint FAO/WHO Expert Committee on Food Additives and various national regulatory bodies have identified factors (called *uncertainty factors* [UFs]) that account for interspecies and intraspecies differences in response to the hazardous effects of substances and for other uncertainties (WHO, 1987). UFs are used to make inferences about the threshold dose of substances for members of a large and diverse human population using data on adverse effects obtained in epidemiological or experimental studies. These factors are applied consistently when data of specific types and quality are available. They are typically used to derive acceptable daily intakes for food additives and other substances for which data on adverse effects are considered sufficient to meet minimum standards of quality and completeness (FAO/WHO, 1982). These adopted or recognized UFs have sometimes been coupled with other factors to compensate for deficiencies in the available data and other uncertainties regarding data.

When possible, the UL is based on a no-observed-adverse-effect level (NOAEL), which is the highest intake (or experimental oral dose) of a nutrient at which no adverse effects have been observed in the individuals studied. This is identified for a specific circumstance in the hazard identification and dose-response assessment steps of the risk. If there are no adequate data demonstrating a NOAEL, then a lowest-observed-adverse-effect level (LOAEL) may be used. A LOAEL is the lowest intake (or experimental oral dose)

at which an adverse effect has been identified. The derivation of a UL from a NOAEL (or LOAEL) involves a series of choices about what factors should be used to deal with uncertainties. Uncertainty factors are applied in an attempt to deal both with gaps in data and with incomplete knowledge about the inferences required (e.g., the expected variability in response within the human population). The problems of both data and inference uncertainties arise in all steps of the risk assessment. A discussion of options available for dealing with these uncertainties is presented below and in greater detail in Appendix K.

A UL is not, in itself, a description or estimate of human risk. It is derived by application of the hazard identification and dose-response evaluation steps (steps 1 and 2) of the risk assessment model. To determine whether populations are at risk requires an intake or exposure assessment (step 3, evaluation of intakes of the nutrient by the population) and a determination of the fractions of these populations, if any, whose intakes exceed the UL. In the intake assessment and risk characterization steps (steps 3 and 4), the distribution of usual intakes for the population is used as a basis for determining whether and to what extent the population is at risk (Figure 3-1). A discussion of other aspects of the risk characterization that may be useful in judging the public health significance of the risk and in risk management decisions is provided in the final section of this chapter, "Risk Characterization."

APPLICATION OF THE RISK ASSESSMENT MODEL TO NUTRIENTS

This section provides guidance for applying the risk assessment framework (the model) to the derivation of Tolerable Upper Intake Levels (ULs) for nutrients.

Special Problems Associated with Substances Required for Human Nutrition

Although the risk assessment model outlined above can be applied to nutrients to derive ULs, it must be recognized that nutrients possess some properties that distinguish them from the types of agents for which the risk assessment model was originally developed (NRC, 1983). In the application of accepted standards for risk assessment of environmental chemicals to risk assessment of nutrients, a fundamental difference between the two categories must be recognized: within a certain range of intakes, nutrients are essential

for human well-being and usually for life itself. Nonetheless, they may share with other chemicals the production of adverse effects at excessive exposures. Because the consumption of balanced diets is consistent with the development and survival of humankind over many millennia, there is less need for the large uncertainty factors that have been used for the risk assessment of nonessential chemicals. In addition, if data on the adverse effects of nutrients are available primarily from studies in human populations, there will be less uncertainty than is associated with the types of data available on nonessential chemicals.

There is no evidence to suggest that nutrients consumed at the recommended intake (the Recommended Dietary Allowance or Adequate Intake) present a risk of adverse effects to the general population.[2] It is clear, however, that the addition of nutrients to a diet through the ingestion of large amounts of highly fortified food or nonfood sources such as supplements or both may (at some level) pose a risk of adverse health effects. The UL is the highest level of daily nutrient intake that is likely to pose no risks of adverse health effects for almost all individuals in the general population. As intake increases above the UL, the risk of adverse effects increases.

If adverse effects have been associated with total intake, ULs are based on total intake of a nutrient from food, water, and supplements. For cases in which adverse effects have been associated with intake only from supplements and food fortificants, the UL is based on intake from those sources only, rather than on total intake. The effects of nutrients from fortified foods or supplements may differ from those of naturally occurring constituents of foods because of the chemical form of the nutrient, the timing of the intake and amount consumed in a single bolus dose, the matrix supplied by the food, and the relation of the nutrient to the other constituents of the diet.

Nutrient requirements and food intake are related to the metabolizing body mass, which is also at least an indirect measure of the space in which the nutrients are distributed. This relation between food intake and space of distribution supports homeostasis, which

[2] It is recognized that possible exceptions to this generalization relate to specific geochemical areas with excessive environmental exposures to certain trace elements (e.g., selenium) and to rare case reports of adverse effects associated with highly eccentric consumption of specific foods. Data from such findings are generally not useful for setting ULs for the general North American population.

maintains nutrient concentrations in that space within a range compatible with health. However, excessive intake of a single nutrient from supplements or fortificants may compromise this homeostatic mechanism. Such elevations alone may pose risks of adverse effects; imbalances among the vitamins may also be possible. These reasons and those discussed previously support the need to include the form and pattern of consumption in the assessment of risk from high nutrient or food component intake.

Consideration of Variability in Sensitivity

The risk assessment model outlined in this chapter is consistent with classical risk assessment approaches in that it must consider variability in the sensitivity of individuals to adverse effects of nutrients or food components. A discussion of how variability is dealt with in the context of nutritional risk assessment follows.

Physiological changes and common conditions associated with growth and maturation that occur during an individual's lifespan may influence sensitivity to nutrient toxicity. For example, sensitivity increases with the declines in lean body mass and with declines in renal and liver function that occur with aging; sensitivity changes in direct relation to intestinal absorption or intestinal synthesis of nutrients; sensitivity in the newborn infant is also increased because of rapid brain growth and limited ability to secrete or biotransform toxicants; and sensitivity increases with decreases in the rate of metabolism of nutrients. During pregnancy, the increase in total body water and glomerular filtration results in lower blood levels of water-soluble vitamins dose for dose and therefore results in reduced susceptibility to potential adverse effects. However, in the unborn fetus this may be offset by active placental transfer, accumulation of certain nutrients in the amniotic fluid, and rapid development of the brain. Examples of life stage groups that may differ in terms of nutritional needs and toxicological sensitivity include infants and children, the elderly, and women during pregnancy and lactation.

Even within relatively homogeneous life stage groups, there is a range of sensitivities to toxic effects. The model described below accounts for normally expected variability in sensitivity but excludes subpopulations with extreme and distinct vulnerabilities. Such subpopulations consist of individuals needing medical supervision; they are better served through the use of public health screening, product labeling, or other individualized health care strategies. Such populations may not be at *negligible risk* when their intakes reach the UL developed for the healthy population. The decision to treat

identifiable vulnerable subgroups as distinct (not protected by the UL) is a matter of judgment and is discussed in individual nutrient chapters as applicable.

Bioavailability

In the context of toxicity, the bioavailability of an ingested nutrient can be defined as its accessibility to normal metabolic and physiological processes. Bioavailability influences a nutrient's beneficial effects at physiological levels of intake and also may affect the nature and severity of toxicity due to excessive intakes. The concentration and chemical form of the nutrient, the nutrition and health of the individual, and excretory losses all affect bioavailability. Bioavailability data for specific nutrients must be considered and incorporated by the risk assessment process.

Some nutrients may be less readily absorbed when they are part of a meal than when consumed separately. Supplemental forms of some nutrients may require special consideration if they have higher bioavailability and therefore may present a greater risk of producing adverse effects than equivalent amounts from the natural form found in food.

Nutrient-Nutrient Interactions

A diverse array of adverse health effects can occur as a result of the interaction of nutrients. The potential risks of adverse nutrient-nutrient interactions increase when there is an imbalance in the intake of two or more nutrients. Excessive intake of one nutrient may interfere with absorption, excretion, transport, storage, function, or metabolism of a second nutrient. Possible adverse nutrient-nutrient interactions are considered as a part of setting a UL. Nutrient-nutrient interactions may be considered either as a critical endpoint on which to base a UL or as supportive evidence for a UL based on another endpoint.

Other Relevant Factors Affecting the Bioavailability of Nutrients

In addition to nutrient interactions, other considerations have the potential to influence nutrient bioavailability, such as the nutritional status of an individual and the form of intake. These issues are considered in the risk assessment. ULs must therefore be based on nutrients as part of the total diet, including the contribution from water. Nutrient supplements that are taken separately from

food require special consideration, because they are likely to have different bioavailabilities and therefore may represent a greater risk of producing adverse effects.

STEPS IN THE DEVELOPMENT OF THE TOLERABLE UPPER INTAKE LEVEL

Hazard Identification

Based on a thorough review of the scientific literature, the hazard identification step outlines the adverse health effects that have been demonstrated to be caused by the nutrient. The primary types of data used as background for identifying nutrient hazards in humans are as follows:

- *Human studies.* Human data provide the most relevant kind of information for hazard identification and, when they are of sufficient quality and extent, are given the greatest weight. However, the number of controlled human toxicity studies conducted in a clinical setting is very limited because of ethical reasons. Such studies are generally most useful for identifying very mild (and ordinarily reversible) adverse effects. Observational studies that focus on well-defined populations with clear exposures to a range of nutrient intake levels are useful for establishing a relationship between exposure and effect. Observational data in the form of case reports or anecdotal evidence are used for developing hypotheses that can lead to knowledge of causal associations. Sometimes a series of case reports, if it shows a clear and distinct pattern of effects, may be reasonably convincing on the question of causality.
- *Animal data.* Most of the available data used in regulatory risk assessments come from controlled laboratory experiments in animals, usually mammalian species other than humans (e.g., rodents). Such data are used in part because human data on nonessential chemicals are generally very limited. Moreover, there is a long-standing history of the use of animal studies to identify the toxic properties of chemical substances, and there is no inherent reason why animal data should not be relevant to the evaluation of nutrient toxicity. Animal studies offer several advantages over human studies. They can, for example, be readily controlled so that causal relationships can be recognized. It is possible to identify the full range of toxic effects produced by a chemical over a wide range of exposures and to establish dose-response relationships. The effects of chronic exposures can be identified in far less time than they can

BOX 3-1 Development of Tolerable Upper Intake Levels (ULs)

COMPONENTS OF HAZARD IDENTIFICATION

- Evidence of adverse effects in humans
- Causality
- Relevance of experimental data
- Pharmacokinetic and metabolic data
- Mechanisms of toxic action
- Quality and completeness of the database
- Identification of distinct and highly sensitive subpopulations

COMPONENTS OF DOSE-RESPONSE ASSESSMENT

- Data selection and identification of critical endpoints
- Identification of no-observed-adverse-effect level (NOAEL) (or lowest-observed-adverse-effect level [LOAEL]) and critical endpoint
- Assessment of uncertainty and data on variability in response
- Derivation of a UL
- Characterization of the estimate and special considerations

be with the use of epidemiological methods. All these advantages of animal data, however, may not always overcome the fact that species differences in response to chemical substances can sometimes be profound, and any extrapolation of animal data to predict human response needs to take into account this possibility.

Key issues that are addressed in the data evaluation of human and animal studies are described below (see Box 3-1).

Evidence of Adverse Effects in Humans

The hazard identification step involves the examination of human, animal, and *in vitro* published evidence addressing the likelihood of a nutrient eliciting an adverse effect in humans. Decisions about which observed effects are adverse are based on scientific judgments. Although toxicologists generally regard any demonstrable structural or functional alteration as representing an adverse effect, some alterations may be considered to be of little or self-limiting biological importance. As noted earlier, adverse nutrient-nutrient interactions are considered in the definition of an adverse effect.

Causality

The identification of a hazard is strengthened by evidence of causality. As explained in Chapter 2, the criteria of Hill (1971) are considered in judging the causal significance of an exposure-effect association indicated by epidemiological studies.

Relevance of Experimental Data

Consideration of the following issues can be useful in assessing the relevance of experimental data.

Animal Data. Some animal data may be of limited utility in judging the toxicity of nutrients because of highly variable interspecies differences in nutrient requirements. Nevertheless, relevant animal data are considered in the hazard identification and dose-response assessment steps where applicable, and, in general, they are used for hazard identification unless there are data demonstrating they are not relevant to human beings or if it is clear that the available human data are sufficient.

Route of Exposure.[3] Data derived from studies involving oral exposure (rather than parenteral, inhalation, or dermal exposure) are most useful for the evaluation of nutrients. Data derived from studies involving parenteral, inhalation, or dermal routes of exposure may be considered relevant if the adverse effects are systemic and data are available to permit interroute extrapolation.

Duration of Exposure. Because the magnitude, duration, and frequency of exposure can vary considerably in different situations, consideration needs to be given to the relevance of the exposure scenario (e.g., chronic daily dietary exposure versus short-term bolus doses) to dietary intakes by human populations.

Pharmacokinetic and Metabolic Data

When available, data regarding the rates of nutrient absorption, distribution, metabolism, and excretion may be important in the derivation of Tolerable Upper Intake Levels (ULs). Such data may provide significant information regarding the interspecies differ-

[3] The terms *route of exposure* and *route of intake* refer to how a substance enters the body (e.g., by ingestion, injection, or dermal absorption). These terms should not be confused with *form of intake*, which refers to the medium or vehicle used (e.g., supplements, food, beverages, or drinking water).

ences and similarities in nutrient behavior and thus may assist with identifying relevant animal data. They may also assist with identifying life-stage differences in response to nutrient toxicity.

In some cases, there may be limited or even no significant data relating to nutrient toxicity. It is conceivable that, in such cases, pharmacokinetic and metabolic data may provide valuable insights into the magnitude of the UL. Thus, if there are significant pharmacokinetic and metabolic data over the range of intakes that meet nutrient requirements, and if it is shown that this pattern of pharmacokinetic and metabolic data does not change in the range of intakes greater than those required for nutrition, it may be possible to infer the absence of toxic risk in this range. In contrast, an alteration of pharmacokinetics or metabolism may suggest the potential for adverse effects. There has been no case encountered thus far in which sufficient pharmacokinetic and metabolic data are available for establishing ULs in this fashion, but it is possible such situations may arise in the future.

Mechanisms of Toxic Action

Knowledge of molecular and cellular events underlying the production of toxicity can assist with addressing the problems of extrapolation between species and from high to low doses. It may also aid in understanding whether the mechanisms associated with toxicity are those associated with deficiency. In most cases, however, because knowledge of the biochemical sequence of events resulting from toxicity and deficiency is still incomplete, it is not yet possible to state with certainty whether these sequences share a common pathway.

Quality and Completeness of the Database

The scientific quality and quantity of the database are evaluated. Human or animal data are reviewed for suggestions that the substances have the potential to produce additional adverse health effects. If suggestions are found, additional studies may be recommended.

Identification of Distinct and Highly Sensitive Subpopulations

The ULs are based on protecting the most sensitive members of the general population from adverse effects of high nutrient intake. Some highly sensitive subpopulations have responses (in terms of

incidence, severity, or both) to the agent of interest that are clearly distinct from the responses expected for the healthy population. The risk assessment process recognizes that there may be individuals within any life stage group who are more biologically sensitive than others, and thus their extreme sensitivities do not fall within the range of sensitivities expected for the general population. The UL for the general population may not be protective for these subgroups. As indicated earlier, the extent to which a distinct subpopulation will be included in the derivation of a UL for the general population is an area of judgment to be addressed on a case-by-case basis.

Dose-Response Assessment

The process for deriving the UL is described in this section and outlined in Box 3-1. It includes selection of the critical data set, identification of a critical endpoint with its no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL), and assessment of uncertainty.

Data Selection and Identification of Critical Endpoints

The data evaluation process results in the selection of the most appropriate or critical data sets for deriving the UL. Selecting the critical data set includes the following considerations:

- Human data, when adequate to evaluate adverse effects, are preferable to animal data, although the latter may provide useful supportive information.
- In the absence of appropriate human data, information from an animal species with biological responses most like those of humans is most valuable. Pharmacokinetic, metabolic, and mechanistic data may be available to assist with the identification of relevant animal species.
- If it is not possible to identify such a species or to select such data, data from the most sensitive animal species, strain, and gender combination are given the greatest emphasis.
- The route of exposure that most resembles the route of expected human intake is preferable. This consideration includes the digestive state (e.g., fed or fasted) of the subjects or experimental animals. Where this is not possible, the differences in route of exposure are noted as a source of uncertainty.
- The critical data set defines a dose-response relationship be-

tween intake and the extent of the toxic response known to be most relevant to humans. Data on bioavailability are considered and adjustments in expressions of dose-response are made to determine whether any apparent differences in response can be explained.

- The critical data set documents the route of exposure and the magnitude and duration of the intake. Furthermore, the critical data set documents the NOAEL (or LOAEL).

Identification of NOAEL (or LOAEL)

A nutrient can produce more than one toxic effect (or endpoint), even within the same species or in studies using the same or different exposure durations. The NOAELs and LOAELs for these effects will ordinarily differ. The critical endpoint used to establish a UL is the adverse biological effect exhibiting the lowest NOAEL (e.g., the most sensitive indicator of a nutrient's toxicity). Because the selection of uncertainty factors (UFs) depends in part on the seriousness of the adverse effect, it is possible that lower ULs may result from the use of the most *serious* (rather than most *sensitive*) endpoint. Thus, it is often necessary to evaluate several endpoints independently to determine which one leads to the lowest UL.

For some nutrients, there may be inadequate data on which to develop a UL. The lack of reports of adverse effects following excess intake of a nutrient does not mean that adverse effects do not occur. As the intake of any nutrient increases, a point (see Figure 3-2) is reached at which intake begins to pose a risk. Above this point, increased intake increases the risk of adverse effects. For some nutrients and for various reasons, there are inadequate data to identify this point or even to estimate its location.

Because adverse effects are almost certain to occur for any nutrient at some level of intake, it should be assumed that such effects may occur for nutrients for which a scientifically documentable UL cannot now be derived. Until a UL is set or an alternative approach to identifying protective limits is developed, intakes greater than the Recommended Dietary Allowance or Adequate Intake should be viewed with caution.

The absence of sufficient data to establish a UL points to the need for studies suitable for developing them.

Uncertainty Assessment

Several judgments must be made regarding the uncertainties and thus the uncertainty factor (UF) associated with extrapolating from

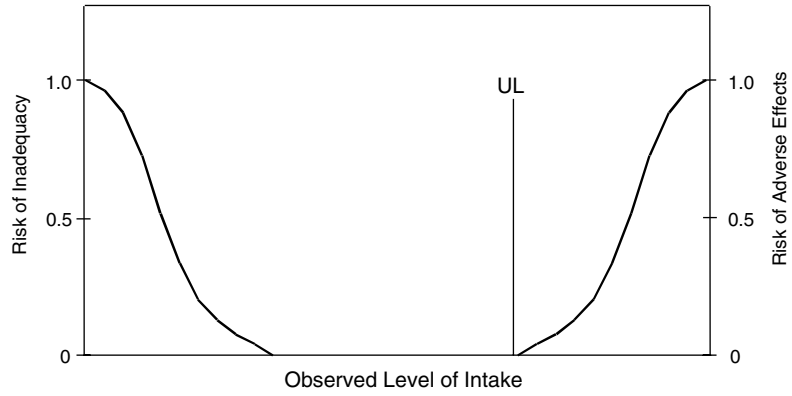

FIGURE 3-2 Theoretical description of health effects of a nutrient as a function of level of intake. The Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risks of adverse health effects for almost all individuals in the general population. At intakes above the UL, the risk of adverse effects increases.

the observed data to the general population (see Appendix K). Applying a UF to a NOAEL (or LOAEL) results in a value for the derived UL that is less than the experimentally derived NOAEL, unless the UF is 1.0. The greater the uncertainty, the larger the UF and the smaller the resulting UL. This is consistent with the ultimate goal of the risk assessment: to provide an estimate of a level of intake that will protect the health of virtually all members of the healthy population (Mertz et al., 1994).

Although several reports describe the underlying basis for UFs (Dourson and Stara, 1983; Zielhuis and van der Kreek, 1979), the strength of the evidence supporting the use of a specific UF will vary. Because the imprecision of these UFs is a major limitation of risk assessment approaches, considerable leeway must be allowed for the application of scientific judgment in making the final determination. Because data are generally available regarding intakes of nutrients in human populations, the data on nutrient toxicity may not be subject to the same uncertainties as are data on nonessential chemical agents. The resulting UFs for nutrients and food components are typically less than the factors of 10 often applied to nonessential toxic substances. The UFs are lower with higher quality data and when the adverse effects are extremely mild and reversible.

In general, when determining a UF, the following potential

sources of uncertainty are considered and combined in the final UF:

- *Interindividual variation in sensitivity.* Small UFs (close to 1) are used to represent this source of uncertainty if it is judged that little population variability is expected for the adverse effect, and larger factors (close to 10) are used if variability is expected to be great (NRC, 1994).
- *Extrapolation from experimental animals to humans.* A UF to account for the uncertainty in extrapolating animal data to humans is generally applied to the NOAEL when animal data are the primary data set available. While a default UF of 10 is often used to extrapolate animal data to humans for nonessential chemicals, a lower UF may be used because of data showing some similarities between the animal and human responses (NRC, 1994).
- *LOAEL instead of NOAEL.* If a NOAEL is not available, a UF may be applied to account for the uncertainty in deriving a UL from the LOAEL. The size of the UF involves scientific judgment based on the severity and incidence of the observed effect at the LOAEL and the steepness (slope) of the dose response.
- *Subchronic NOAEL to predict chronic NOAEL.* When data are lacking on chronic exposures, scientific judgment is necessary to determine whether chronic exposure is likely to lead to adverse effects at lower intakes than those producing effects after subchronic exposures (exposures of shorter duration).

Derivation of a UL

The UL is derived by dividing the NOAEL (or LOAEL) by a single UF that incorporates all relevant uncertainties. ULs, expressed as amount per day, are derived for various life stage groups using relevant databases, NOAELs, LOAELs, and UFs. In cases where no data exist with regard to NOAELs or LOAELs for the group under consideration, extrapolations from data in other age groups or animal data are made on the basis of known differences in body size, physiology, metabolism, absorption, and excretion of the nutrient.

Generally, any age group adjustments are made based solely on differences in body weight, unless there are data demonstrating age-related differences in nutrient pharmacokinetics, metabolism, or mechanism of action.

The derivation of the UL involves the use of scientific judgment to select the appropriate NOAEL (or LOAEL) and UF. As shown in

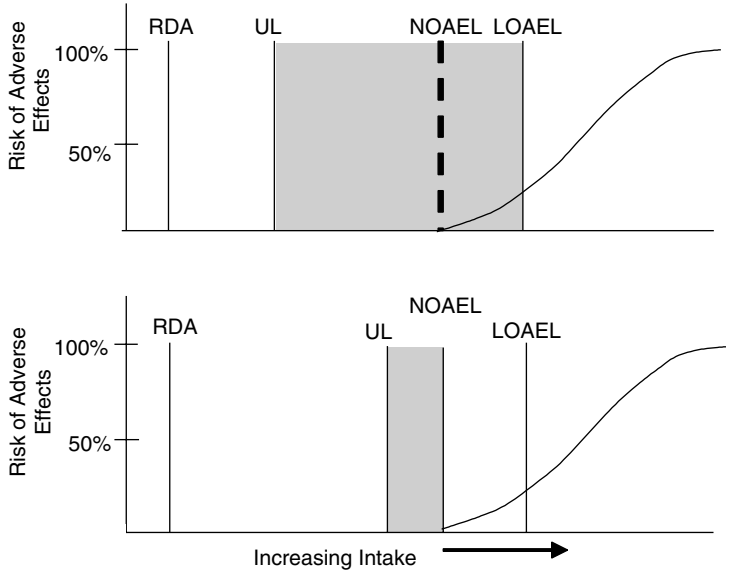

FIGURE 3-3 Effect of uncertainty assessment on UL. Dashed line represents hypothetical NOAEL. Solid lines represent available data used to set the UL. The gray area represents theoretical range of uncertainty. UL = Tolerable Upper Intake Level; NOAEL = no-observed-adverse-effect level; LOAEL = lowest-observed-adverse-effect level; RDA = Recommended Dietary Allowance.

Figure 3-3, when using the same critical endpoint there is a greater level of uncertainty in setting the UL based on a LOAEL as compared with a NOAEL. The risk assessment requires explicit consideration and discussion of all choices made, regarding both the data used and the uncertainties accounted for. These considerations are discussed in the chapters on nutrients and food components.

Characterization of the Estimate and Special Considerations

If the data review reveals the existence of subpopulations having distinct and exceptional sensitivities to a nutrient's toxicity, these subpopulations are explicitly discussed and concerns related to adverse effects are noted; however, the use of the data is not included in the identification of the NOAEL or LOAEL on which the UL for the general population is based.

Circumstances in Which No UL Is Established

There are two general conditions under which ULs are not established. In some cases the lack of sufficient evidence regarding a nutrient's capacity to cause adverse effects prohibits the application of the UL model. In other cases, the evidence is available but meeting the UL derived from such evidence will necessarily result in the introduction of undesirable health effects because of the required adjustments in dietary patterns.

Insufficient Evidence of Adverse Effects

The scientific evidence relating to adverse effects of nutrient excess varies greatly among nutrients. The type of data and evidence of causation used to derive ULs have been described in the earlier sections of this chapter, but such data and evidence are simply unavailable for some nutrients. In some cases, some data relating to adverse effects may be available but are of such uncertain relevance to human health that their use in deriving ULs is scientifically insupportable. In every instance in which ULs are not derived because of lack of adequate evidence, the specific limitations in the database are described.

INTAKE ASSESSMENT

To assess the risk of adverse effects, information on the range of nutrient intakes in the general population is required. As noted earlier, in cases where the Tolerable Upper Intake Level pertains only to supplement use and does not pertain to usual food intakes of the nutrient, the assessment is directed at supplement intakes only.

RISK CHARACTERIZATION

As described earlier, the question of whether nutrient intakes create a risk of toxicity requires a comparison of the range of nutrient intakes (food, supplements, and other sources or supplements alone, depending on the basis for the Tolerable Upper Intake Level [UL]) with the UL.

Figure 3-4 illustrates a distribution of chronic nutrient intakes in a population; the fraction of the population experiencing chronic intakes above the UL represents the potential at-risk group. A policy decision is needed to determine whether efforts should be made

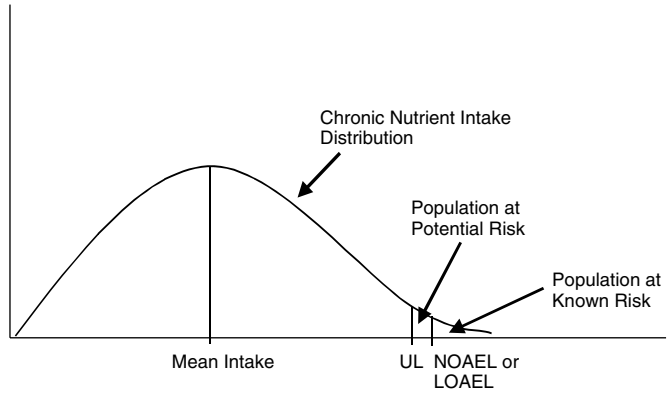

FIGURE 3-4 Illustration of the population at risk from excessive nutrient intakes. The fraction of the population consistently consuming a nutrient at intake levels in excess of the UL is potentially at risk of adverse health effects. See text for a discussion of additional factors necessary to judge the significance of the risk. LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; UL = Tolerable Upper Intake Level.

to reduce risk. Few precedents for nutrients are available for such policy choices, although in the area of food additive or pesticide regulation, federal regulatory agencies have generally sought to ensure that the ninetieth or ninety-fifth percentile intakes fall below the UL (or its approximate equivalent measure of risk). If this goal is achieved, the fraction of the population remaining above the UL is likely to experience intakes only slightly greater than the UL and is likely to be at little or no risk.

For risk management decisions, it is useful to evaluate the public health significance of the risk, and information contained in the risk characterization is critical for that purpose.

Thus, the significance of the risk to a population consuming a nutrient in excess of the UL is determined by the following:

1. the fraction of the population consistently consuming the nutrient at intake levels in excess of the UL,
2. the seriousness of the adverse effects associated with the nutrient,
3. the extent to which the effect is reversible when intakes are reduced to levels less than the UL, and

4. the fraction of the population with consistent intakes above the NOAEL or even the LOAEL.

Thus, the significance of the risk of excessive nutrient intake cannot be judged only by reference to Figure 3-4, but requires careful consideration of all of the above factors. Information on these factors is contained in this report's sections describing the bases for each of the ULs.

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4
Water

SUMMARY

Water is the largest single constituent of the human body and is essential for cellular homeostasis and life. *Total* water intake includes drinking water, water in beverages, and water that is part of food. Although a low intake of *total* water has been associated with some chronic diseases, this evidence is insufficient to establish water intake recommendations as a means to reduce the risk of chronic diseases. Instead, an Adequate Intake (AI) for *total* water is set to prevent deleterious, primarily acute, effects of dehydration, which include metabolic and functional abnormalities.

The primary indicator of hydration status is plasma or serum osmolality. Because normal hydration can be maintained over a wide range of water intakes, the AI for *total* water (from a combination of drinking water, beverages, and food) is set based on the median *total* water intake from U.S. survey data. The AI for *total* water intake for young men and women (ages 19 to 30 years) is 3.7 L and 2.7 L per day, respectively.[1] Fluids (drinking water and beverages) provided 3.0 L (101 fluid oz; ≈ 13 cups) and 2.2 L (74 fluid oz; ≈ 9 cups) per day for 19- to 30-year-old men and women, respectively, representing approximately 81 percent of *total* water intake in the U.S. survey. Water contained in food provided ap-

[1] Conversion factors: 1 L = 33.8 fluid oz; 1 L = 1.06 qt; 1 cup = 8 fluid oz.

proximately 19 percent of *total* water intake. Canadian survey data indicated somewhat lower levels of *total* water intake. As with AIs for other nutrients, for a healthy person, daily consumption below the AI may not confer additional risk because a wide range of intakes is compatible with normal hydration. In this setting, the AI should not be interpreted as a specific requirement. Higher intakes of *total* water will be required for those who are physically active or who are exposed to hot environments.

Over the course of a few hours, body water deficits can occur due to reduced intake or increased water losses from physical activity and environmental (e.g., heat) exposure. However, on a day-to-day basis, fluid intake, driven by the combination of thirst and the consumption of beverages at meals, allows maintenance of hydration status and total body water at normal levels.

Because healthy individuals have considerable ability to excrete excess water and thereby maintain water balance, a Tolerable Upper Intake Level (UL) was not set for water. However, acute water toxicity has been reported due to rapid consumption of large quantities of fluids that greatly exceeded the kidney's maximal excretion rate of approximately 0.7 to 1.0 L/hour.

BACKGROUND INFORMATION

Water, which is the solvent for biochemical reactions, has unique physical properties (e.g., high specific heat) to absorb metabolic heat within the body. Water is also essential for maintaining vascular volume and serves as the medium for transport within the body by supplying nutrients and removing waste. In addition, cell hydration has been has been suggested to be an important signal to regulate cell metabolism and gene expression (Haussinger et al., 1994). Daily water intake must be balanced with losses in order to maintain total body water. Body water deficits challenge the ability to maintain homeostasis during perturbations (e.g., sickness, physical exercise, and environmental exposure) and can affect function and health. In very unusual circumstances, excess consumption of hypotonic fluids and low sodium intake may lead to excess body water, resulting in hyponatremia and cellular edema.

Despite the importance of adequate water intake, there is confusion among the general public and health care providers on the amount of water that should be consumed (Valtin, 2002), in part because of misinterpretation of previous recommendations (NRC, 1989).

BODY WATER

Fat-Free Mass

Body water volume, as a percentage of fat-free mass, is highest in infants and declines in older children (Fomon, 1967; Van Loan and Boileau, 1996). High body water volume is particularly evident in newborns, whose body water content of fat-free mass may exceed 75 percent (Fomon, 1967). Infants also have a relatively higher water content in the extracellular compartment and a lower water content in the intracellular compartment compared with older children (Van Loan and Boileau, 1996). Figure 4-1 presents total body water as a percentage of fat-free mass and body mass in children through the teenage years. Total body water as percentage of fat-free mass decreases during childhood, albeit more slowly than in infancy.

For adults, fat-free mass is approximately 70 to 75 percent water, and adipose tissue is approximately 10 to 40 percent water. With increasing fatness, the water fraction of adipose tissue decreases (Martin et al., 1994). Figures 4-2 and 4-3 provide the percentage of

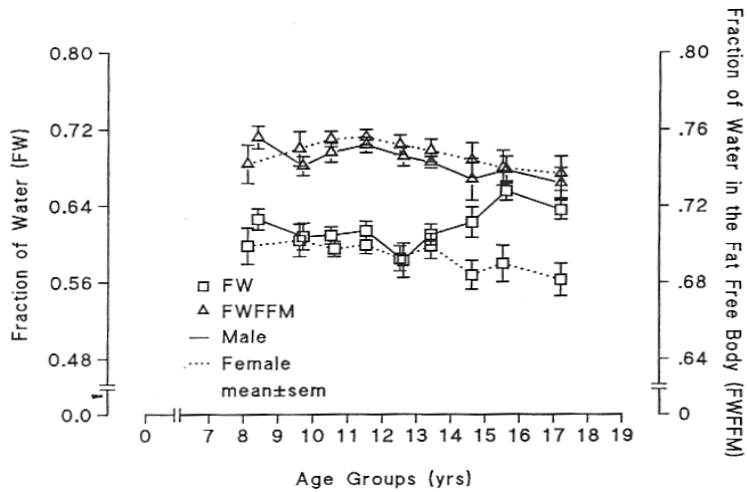

FIGURE 4-1 Total body water as a fraction of body mass (FW) and as a fraction of fat-free mass (FWFFM). Reprinted with permission, from Van Loan and Boileau (1996). Copyright 1996 by CRC Press.

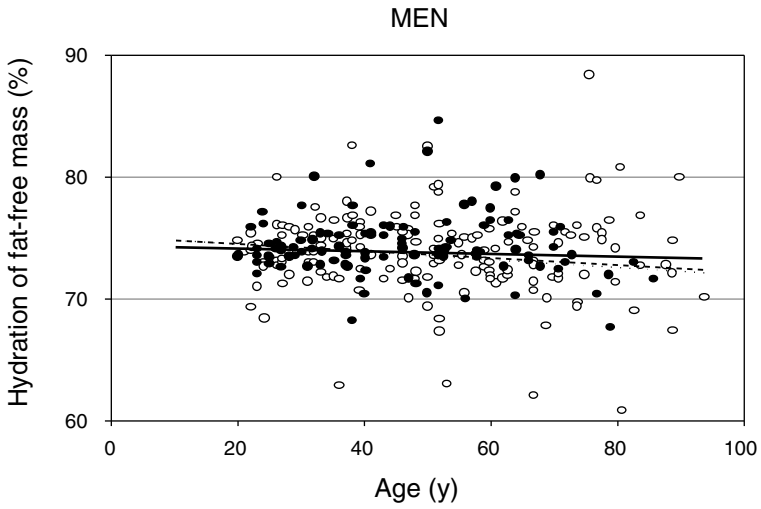

FIGURE 4-2 Hydration of fat-free mass in relation to age for 95 African-American (closed circles) and 204 white (open circles) men. Reprinted with permission, from Visser and Gallagher (1998). Copyright 1998 by John Libbey Eurotext.

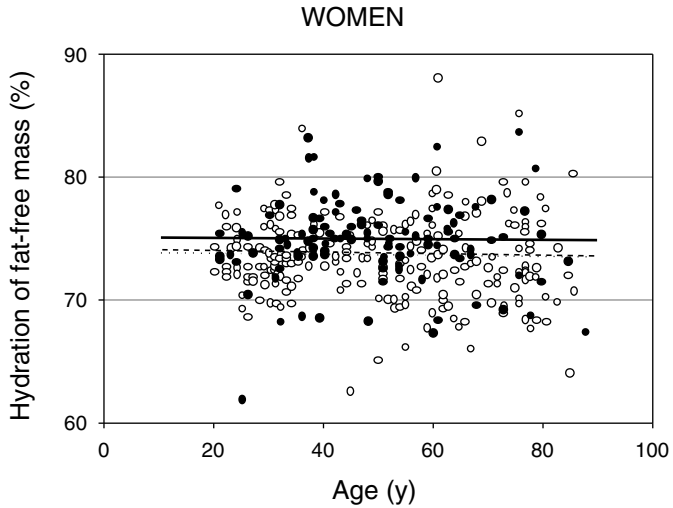

FIGURE 4-3 Hydration of fat-free mass in relation to age for 99 African-American (closed circles) and 270 white (open circles) women. Reprinted with permission, from Visser and Gallagher (1998). Copyright 1998 by John Libbey Eurotext.

water (tritiated water) in fat-free mass measured by dual energy X-ray absorptiometry (DEXA) in relation to age for men and women, respectively (Visser and Gallagher, 1998; Visser et al., 1997). Note that individual variation exists for the hydration of fat-free tissue and values remain relatively stable with increasing age. Neither ethnicity nor gender altered the hydration of fat-free mass. Similar values were reported for whites (men = 74 percent, women = 74 percent) and African Americans (men = 75 percent, women = 75 percent). Other investigators have supported the observation that age and gender do not markedly alter the hydration of fat-free mass in adults (Baumgartner et al., 1995; Goran et al., 1994; Mazariegos et al., 1994).

Total Body Water

Total body water (TBW), comprising extracellular fluid (ECF) and intracellular fluid (ICF), averages approximately 60 percent of body weight, with a range from approximately 45 to 75 percent (Altman, 1961). Variability in TBW is primarily due to differences in body composition. TBW is usually measured by volume distribution of an appropriate indicator (e.g., antipyrine, deuterium oxide, tritium oxide). Table 4-1 provides TBW values for different age and gender groups based upon indicator dilution methods (Altman, 1961). Women and older persons have reduced TBW primarily because of having lower fat-free mass and increased body fat. Gender

TABLE 4-1 Total Body Water (TBW) as a Percentage of Total Body Weight in Various Age and Gender Groups

Lifestage	TBW as a Percentage of Body Weight, Mean (range)
0–6 mo	74 (64–84)
6 mo–1 yr	60 (57–64)
1–12 yr	60 (49–75)
Males, 12–18 yr	59 (52–66)
Females, 12–18 yr	56 (49–63)
Males, 19–50 yr	59 (43–73)
Females, 19–50 yr	50 (41–60)
Males, 51+ yr	56 (47–67)
Females, 51+ yr	47 (39–57)

SOURCE: Altman (1961).

differences in TBW are not observed until after approximately 12 years of age (Novak, 1989), when boys start increasing their fat-free mass at a rate faster than girls do.

Athletes have relatively high TBW values by virtue of having a high fat-free mass, low body fat, and high skeletal muscle glycogen levels. High skeletal muscle glycogen levels increase the water content of fat-free tissue due to osmotic pressure exerted by glycogen granules within the muscle sarcoplasm (Neufer et al., 1991; Olsson and Saltin, 1970).

Distribution

Body water is distributed between the ICF and the ECF, which contain 65 and 35 percent of TBW, respectively. The ECF is further divided into the interstitial and plasma spaces. An average 70-kg man has approximately 42 L of total body water, 28 L of ICF, and 14 L of ECF, with the ECF comprising approximately 3 L of plasma and 11 L of interstitial fluid. These are not static volumes, but represent the net effects of dynamic fluid exchange with varying turnover rates between compartments (Guyton and Hall, 2000). Perturbations such as exercise, heat exposure, fever, diarrhea, trauma, and skin burns will greatly modify the net volumes and water turnover rates between these fluid compartments.

Exchange

Water exchange between the ICF and ECF depends on osmotic gradients. Water passes through membranes from regions of lower to higher solute concentration by osmosis, which attempts to equalize the concentration differences across the membrane. Cell membranes are freely permeable to water, but they are only selectively permeable to solutes. Water thus distributes across cell membranes to equalize the osmotic concentrations of extracellular and intracellular fluids. Although the two compartments contain different individual solute concentrations, the total equilibrium concentration of cations and anions is the same in each compartment as described by the Gibbs-Donnan equilibrium. In the ECF, the most abundant cation is sodium, while chloride and bicarbonate are the primary anions. These ions represent 90 to 95 percent of the osmotically active components of the ECF, and changes in their content alter the ECF volume. In the ICF, the most abundant cations are potassium and magnesium, while proteins are the primary anions. The marked differences in sodium and potassium concentrations be-

tween ICF and ECF are maintained by active transport-mediated ion pumps within cell membranes.

Water exchange between the intravascular and interstitial spaces occurs in the capillaries. Capillaries of different tissues have varied anatomic structures and therefore different permeability to water and solutes. The transcapillary forces that determine if net filtration (i.e., water leaving the vascular space) or net absorption (i.e., water entering the vascular space) will occur are hydrostatic and oncotic pressures. Oncotic pressure is the osmotic pressure attributed to serum protein concentration (e.g., serum albumin levels) differences across the capillary membrane. Generally, filtration occurs at the arterial end of the capillary, while absorption occurs at the venous end.

Incomplete fluid replacement resulting in decreased total body water affects each fluid space as a consequence of free fluid exchange (Costill and Fink, 1974; Durkot et al., 1986; Nose et al., 1983). The distribution of body water loss among the fluid spaces, as well as among different body organs during water deficit (dehydration or hypohydration), was determined in an animal model (Nose et al., 1983). The fluid deficit in rats thermally dehydrated by 10 percent of body weight was apportioned between the intracellular (41 percent) and extracellular (59 percent) spaces. Organ fluid loss was 40 percent coming from muscle, 30 percent from skin, 14 percent from viscera, and 14 percent from bone. Neither the brain nor liver lost significant water content. Various dehydration methods influence the partitioning of water loss from the fluid spaces (Mack and Nadel, 1996).

Determinants of Body Water Balance

Body water balance depends on the net difference between water gain and water loss. Water gain occurs from consumption (liquids and food) and production (metabolic water), while water losses occur from respiratory, skin, renal, and gastrointestinal tract losses. Water is normally consumed by mouth via liquid and food, and this mixture is digested and absorbed within the gastrointestinal tract. Therefore, water intake can be estimated from measured liquid volumes and tables of food composition. Water losses can be estimated from a variety of physiological and biophysical measurements and calculations (Adolph, 1933; Consolazio et al., 1963; Johnson, 1964). Depending upon a person's age, health, diet, activity level, and environmental exposure, different physiological and biophysical methods can be used to quantify the water balance components. Table

TABLE 4-2 Estimation of Minimum Daily Water Losses and Production[a]

Reference	Source	Loss (mL/d)	Production (mL/d)
Hoyt and Honig, 1996	Respiratory loss	–250 to –350	
Adolph, 1947b	Urinary loss	–500 to –1,000	
Newburgh et al., 1930	Fecal loss	–100 to –200	
Kuno, 1956	Insensible loss	–450 to –1,900	
Hoyt and Honig, 1996	Metabolic production		+250 to +350
	Total	–1,300 to –3,450	+250 to +350
	Net loss	–1,050 to –3,100	

[a] Assuming conditions in which there is minimal water loss from sweating.

4-2 displays estimated minimum losses and production of water (mL/day) in healthy sedentary adults, assuming conditions in which there is minimal water loss from thermoregulatory sweating. The following sections describe each source of water loss or production listed in this table.

Respiratory Water Loss

The amount of respiratory water loss, via evaporation within the lungs, is dependent on both the ventilatory volume and water vapor pressure gradient (Mitchell et al., 1972). Ventilatory volume is increased by physical activity, hypoxia, and hypercapnia, whereas the water vapor pressure is modified by the ambient temperature, humidity, and barometric pressure. Physical activity generally has a greater effect on respiratory water loss than do environmental factors. Daily respiratory water loss averages about 250 to 350 mL/day for sedentary persons, but can increase to 500 to 600 mL/day for active persons living in temperate[2] climates at sea level (Hoyt and Honig, 1996). For these conditions, respiratory water loss (y = mL/day) can be predicted from metabolic rate (x = kcal/day) by the equation y = 0.107x + 92.2 (Hoyt and Honig, 1996). High altitude exposure (greater than 4,300 m, 448 mm Hg) can further increase respiratory water losses by approximately 200 mL/day (Hoyt and Honig, 1996).

[2] In general, dry bulb temperatures of approximately 70°F, 80°F, and 90°F are used for temperate, warm, and hot conditions, respectively, in this report.

Ambient air temperature and humidity modify respiratory water losses. Breathing hot, dry air during intense physical exercise can increase respiratory water losses by 120 to 300 mL/day (Mitchell et al., 1972). Breathing cold, dry air during rest and stressful physical exercise (Table 4-3) can increase respiratory water losses by approximately 5 mL/hour and approximately 15 to 45 mL/hour, respectively (Freund and Young, 1996). Freund and Young (1996) have calculated that for a 24-hour military scenario (8 hours of rest, 12 hours of moderate activity, and 4 hours of moderate-heavy activity), the respiratory water losses increase by approximately 340 mL/day when breathing –20°C versus +25°C air.

Urinary and Gastrointestinal Water Loss

The kidneys are responsible for regulating the volume and composition of the ECF via a series of intricate neuroendocrine pathways (Andreoli et al., 2000). Renal fluid output can vary depending upon the specific macronutrient, salt, and water load. However, for persons consuming an average North American diet, some of these effects may not be discernable (Luft et al., 1983). Since there is a limit to how much the kidneys can concentrate urine, the minimal amount of water needed is determined by the quantity of end products that need to be excreted (e.g., creatinine, urea). On typical Western diets, an average of 650 mOsmol of electrolytes and other

TABLE 4-3 Influence of Breathing Cold Air and of Metabolic Rate on Respiratory Water Losses

Temperature		Relative Humidity	Water Vapor Pressure	Metabolic Rate	Respiratory Water Loss
°F	°C	(%)	(mm Hg)	(Watts)	(mL/h)
77	25	65	15	Rest (100)	≈ 10
32	0	100	5	Rest (100)	≈ 13
–4	–20	100	1	Rest (100)	≈ 15
77	25	65	15	Light-moderate (300)	≈ 30
32	0	100	5	Light-moderate (300)	≈ 40
–4	–20	100	1	Light-moderate (300)	≈ 45
77	25	65	15	Moderate-heavy (600)	≈ 60
32	0	100	5	Moderate-heavy (600)	≈ 80
–4	–20	100	1	Moderate-heavy (600)	≈ 90

SOURCE: Reprinted with permission, from Freund and Young (1996). Copyright 1996 by CRC Press.

solutes must be excreted per day to maintain electrolyte balance; thus, if the urine is maximally concentrated (U_{osm} approximately 1,200 mOsmol/kg water), the minimum urine output is approximately 500 mL/day. For dehydrated subjects living in hot weather, minimum daily urine outputs can be less than 500 mL/day (Adolph, 1947b).

Urine output generally averages 1 to 2 L/day but can reach 20 L/day in those consuming large quantities of fluid (West, 1990). Healthy older individuals, however, cannot concentrate urine as well as young individuals and thus have a higher minimum urine output. For example, older men and women (mean age 79 years) had lower maximal urine osmolalities of 808 and 843 mOsm/kg, respectively, compared with 1,089 mOsm/kg for young men (mean age 24 years). This corresponds to higher minimum urine outputs of 700 and 1,086 mL/day for the older men and women compared with 392 mL/day for the young men (Dontas et al., 1972).

Urine output varies inversely with body hydration status. Figure 4-4 depicts the hyperbolic relationship between urine output and

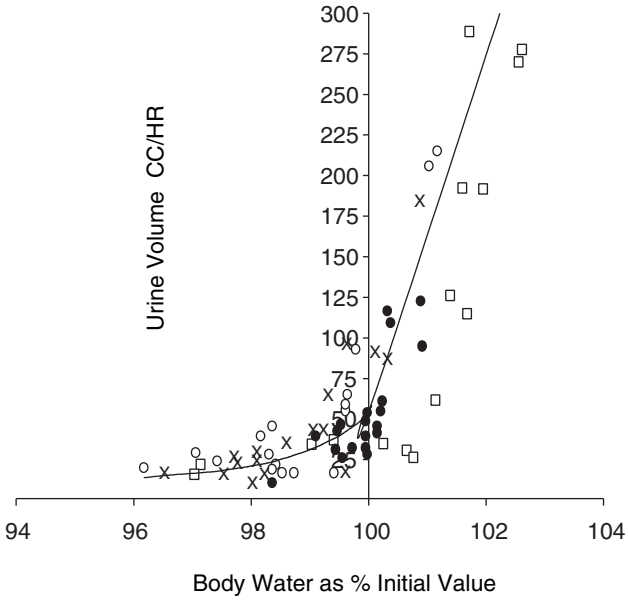

FIGURE 4-4 Relation of urine output to body hydration status. Reprinted with permission, from Lee (1964). Copyright 1964 *Handbook of Physiology, Section 4*, American Physiological Society.

body hydration status: one asymptote ascends steeply with hyperhydration, while the other descends gradually with dehydration (Lee, 1964). The apex of this hyperbolic relationship approximates a urine output of approximately 50 mL/hour. The extremes depicted in Figure 4-4 can be exceeded. For example, investigators have reported that urine output can transiently increase to approximately 600 to 1,000 mL/hour with water loading (Freund et al., 1995; Noakes et al., 2001; Speedy et al., 2001) and decrease to approximately 15 mL/hour with dehydration (Adolph, 1947b). Urine output can vary widely to maintain total body water; however, there are clearly limits to the amount of conservation and excretion.

Physical activity and climate also affect urine output. Exercise and heat strain will reduce urine output by 20 to 60 percent (Convertino, 1991; Mittleman, 1996; Zambraski, 1996), while cold and hypoxia will increase urine output (Freund and Young, 1996; Hoyt and Honig, 1996).

Gastrointestinal and thus fecal water loss in healthy adults is approximately 100 to 200 mL/day (Newburgh et al., 1930).

Insensible and Sweat Losses

Water loss through the skin occurs via insensible diffusion and secreted sweat. For the average adult, loss of water by insensible diffusion is approximately 450 mL/day (Kuno, 1956). During heat stress, eccrine sweat glands secrete sweat onto the skin surface, which cools the body when water evaporates from the sweat. In hot weather, sweat evaporation provides the primary avenue of heat loss to defend the body's core temperature. When a gram of sweat water is vaporized at 30°C, 2.43 kJ (0.58 kcal) of heat becomes kinetic energy (latent heat of evaporation) (Wenger, 1972). For a given hot weather condition, the required sweating rate for evaporative cooling is dependent upon the physical activity level (metabolic rate).

The following calculations provide the minimal sweat produced by persons performing moderately heavy (metabolic rate ≈ 600 W) exercise in the heat (Sawka et al., 1996a). If the activity is 20 percent efficient, the remaining 80 percent of metabolic energy produced is converted to heat in the body so that 480 W (0.48 kJ/second, or 28.8 kJ/minute or 6.88 kcal/minute) need to be dissipated to avoid heat storage. The specific heat of body tissue (amount of energy required for 1 kg of tissue to increase temperature by 1°C) approximates 3.5 kJ (0.84 kcal)/kg/°C. For example, a 70-kg man has a heat capacity of 245 kJ (59 kcal)/°C, and a 50-kg woman has a heat capacity of 173

kJ (41 kcal)/°C. If these persons performed exercise in a hot environment that enabled only evaporative heat loss and they did not sweat, their body temperatures would increase by approximately 1.0°C every 8.5 min for the man (245 kJ/°C ÷ 28.8 kJ/minute *or* 59 kcal/°C ÷ 6.88 kcal/minute) and every 6 minutes for the woman (173 kJ/°C ÷ 28.8 kJ/minute *or* 41 kcal/°C ÷ 6.88 kcal/minute). Since the latent heat of evaporation is 2.43 kJ/g (0.58 kcal/g), such persons would need to evaporate approximately 12 g of sweat per minute (28.8 kJ/minute ÷ 2.43 kJ/g *or* 6.88 kcal/minute ÷ 0.58 kcal/g) or 0.72 L/hour. Because secreted sweat drips from the body and is not evaporated, higher sweat secretions are often needed to achieve these cooling demands. If a person is physically active and exposed to environmental heat stress, sweat losses to avoid heat storage can be substantial over a 24-hour period.

For persons living in hot climates, daily sweat losses often exceed several liters. As described above, daily sweat losses are determined by the evaporative heat loss requirements, which are influenced by the metabolic rate (above example) and environment. The environmental factors that modify sweat losses include clothing worn, ambient temperature, humidity, air motion, and solar load. Therefore, considerable variability will exist for daily sweat losses among different people. Figure 4-5 provides the distribution of daily sweat-

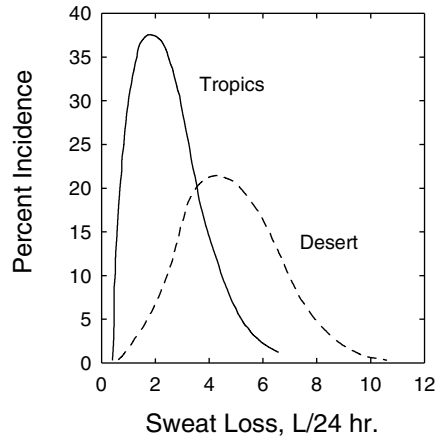

FIGURE 4-5 Distribution of daily sweating rates for active soldiers in desert and tropical climates. Percent incidence refers to the percentage of the subject population achieving the given daily sweat loss.
SOURCE: Molnar (1947). Reprinted with permission from the Papers of Edward Adolph collection at the Edward G. Miner Library, University of Rochester Medical Center.

ing rates for soldiers living in desert and tropical climates (without air conditioning). The average daily sweat loss for 97 men in the desert was 4.9 L; for 26 men in the tropics, it was 2.3 L. The lower daily sweat losses in the tropics were probably due to lower ambient temperatures and lower solar load (both acting to lower the required evaporative cooling), as the precise activity levels of both groups were unknown.

Metabolic Water Production

Metabolic water is formed by oxidation of hydrogen-containing substrates during metabolism or energy-yielding nutrients. Oxidation of carbohydrate, protein, and fat produces metabolic water of approximately 15, 10.5, and 11.1 g/100 kcal of metabolizable energy, respectively (Lloyd et al., 1978). Therefore, metabolic water production is proportional to the energy expenditure with a small adjustment for the substrate oxidized. Figure 4-6 shows the metabolic water production relative to daily energy expenditure for persons eating a mixed diet (Hoyt and Honig, 1996). If the regression line in Figure 4-6 is extrapolated to the daily energy expenditures of ≈ 2,500 kcal/day, the metabolic water production will approximate 250 mL/day. Therefore, a reasonable estimate of daily metabolic

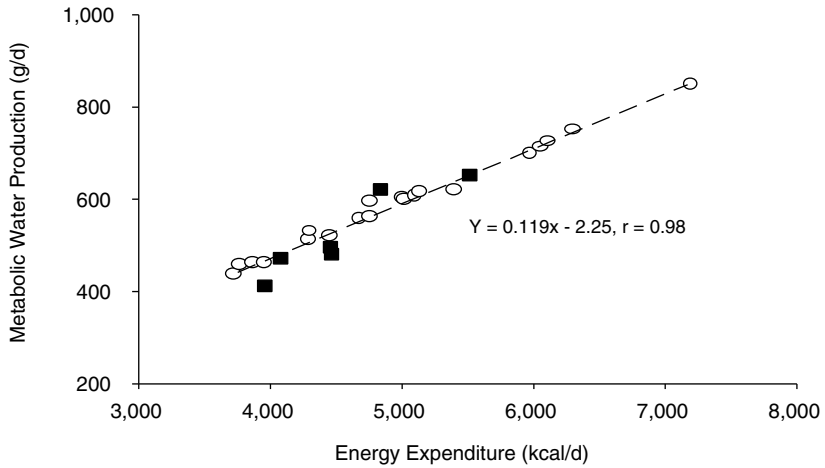

FIGURE 4-6 Metabolic water production relative to daily energy expenditure. Reprinted with permission, from Hoyt and Honig (1996). Copyright 1996 by CRC Press.

water production is an average of approximately 250 to 350 L/day for sedentary persons—but which can increase to 500 to 600 mL/day for physically active persons (Hoyt and Honig, 1996). Hence, respiratory water losses are roughly equivalent to, or offset by, metabolic water production (Table 4-2; Hoyt and Honig, 1996). Metabolic water, a by-product of metabolizing energy-yielding nutrients from foods into carbon dioxide and energy, does not include the water present in a foodstuff itself. This is considered compositional water, or moisture. It is often determined analytically as the difference in weight of a food item before and after drying to a constant weight.

Consumption

Fluid is consumed in the form of food and beverages, and, regardless of form, is absorbed by the gastrointestinal tract and acts the same physiologically. In one survey of the adult U.S. population (1977–1978 Nationwide Food Consumption Survey), total water intake was approximately 28 percent from foods, 28 percent from drinking water, and 44 percent from other beverages (Ershow and Cantor, 1989). National survey data for adults (Appendix Tables D-1, D-3, and D-4) likewise suggest that approximately 20 percent of water comes from food, and the remaining 80 percent comes from fluids.

Drinking induced by water deprivation is homeostatic (Greenleaf and Morimoto, 1996). Other factors (e.g., social, psychological) that influence drinking behavior are nonregulatory (Rolls and Rolls, 1982). Over an extended period, fluid consumption will match body water needs (if adequate amounts are available). However, mismatches can occur over short periods (Johnson, 1964). The fluid intake for healthy adults can vary markedly depending on activity level, environmental exposure, diet, and social activities; nonetheless, for a given set of conditions, intake is reproducible within persons (Johnson, 1964). Therefore, it is reasonable to assume that for large population studies of apparently healthy individuals, the fluid volume consumed is equal to or greater than body water needs.

METHODS FOR ESTIMATING WATER REQUIREMENTS

Water Balance

Water balance is regulated within ± 0.2 percent of body weight over a 24-hour period for healthy adults at rest (Adolph, 1943).

Adolph (1943) described the rates of water gain and water loss relative to different levels of water deficit and excess. Induced water deficits or water excesses resulted in compensatory changes in water gains and water losses until water balance was reestablished. Likewise, Newburgh and colleagues (1930) demonstrated the accuracy of water balance studies to be within 0.5 percent of the water volume. Therefore, *ad libitum* water balance studies can be used to estimate daily water requirements, provided the subjects have adequate time for rehydration and physiologic compensation (Adolph, 1943; Newburgh et al., 1930). In both these studies, total water intake was measured.

Table 4-4 presents water balance studies that have estimated daily total water requirements for infants and children. Note that daily total water requirements increase with age from early infancy (approximately 0.6 L) through childhood (approximately 1.7 L). Since infants have rapid growth, some investigators express the daily water needs relative to body mass.

The minimal daily water requirement depends upon the person's diet, environment, and activity level. After reviewing early water balance studies, Adolph (1933) concluded that for most adult men,

TABLE 4-4 Estimation of Daily Water Requirements of Infants and Children from Water Balance Studies

Reference	Subjects (age)	Conditions	Total Volume Intake, L/d (mL/kg/d)	Total Water Intake, L/d (mL/kg/d)
Goellner et al., 1981		Normal activity		
15 infants	10 studies, 0–1 mo		0.66 (184)	0.56 (156)[a]
	9 studies, 1–2 mo		1.00 (199)	0.85 (170)
	14 studies, 2–4 mo		0.94 (161)	0.79 (137)
	18 studies, 4–6 mo		1.13 (162)	0.96 (138)
	39 studies, 6–12 mo		1.31 (158)	1.11 (135)
	24 studies, 12–18 mo		1.57 (146)	1.33 (124)
	21 studies, 18–24 mo		1.55 (129)	1.32 (110)
	15 studies, 24–32 mo		1.62 (117)	1.38 (99)
Ballauff et al., 1988	21 children, 6–11 yr	Normal activity		≈ 1.7 for boys ≈ 1.5 for girls

[a] Goellner et al. (1981) estimated that water accounted for 85 percent or more of the determined volume intake. Thus total water intake was calculated as 85 percent of total volume intake.

the minimal, average, and liberal water requirements approximated 2.1, 3.4, and 5.0 L/day, respectively. In addition, Adolph (1933) concluded that a convenient "liberal standard" for total water intake is 1 mL/kcal expended. Subsequent studies by Johnson (1964) recommended minimum daily water requirements of no less then 0.91 L for survival conditions and 3.0 L for hot weather.

Table 4-5 presents water balance studies that have estimated daily total water requirements for adults. These requirements are above minimal levels because some physical activity (although usually nominal) was allowed and because individuals self-selected the volume of consumed fluids (i.e., *ad libitum* water consumption). For the prolonged bed-rest studies, greater emphasis was placed on data obtained during the initial week, if available. Water balance studies suggest that the required water intake to maintain water balance for resting adult men is approximately 2.5 L/day (Adolph, 1933; Newburgh et al., 1930). If modest physical activity is performed, the

TABLE 4-5 Estimation of Daily Water Requirements of Adults from Water Balance Studies

Reference	Subjects	Conditions	Total Water Intake (L/d)
Women			
Yokozawa et al., 1993	3 women	Temperate, bed-rest	≈ 1.6
Men			
Newburgh et al., 1930	Repeated studies of men	Temperate, rest, variety of diets	≈ 2.6
Welch et al., 1958	53 men	Active, ambient temperature range of –30°C to +30°C	≈ 3.0 at –20°C to +20°C ≈ 6.0 at +30°C
Consolazio et al., 1967	6 men	Temperate, rest, starvation study	≈ 2.5 (1st 4 d; ~ 3.4 if corrected for negative balance)
Consolazio et al., 1968	24 men	Temperate, rest, sea level controls	≈ 2.5
Greenleaf et al., 1977	7 men	Temperate, bed-rest with 1 h of exercise/d	≈ 3.2
Gunga et al., 1993	6 men	Temperate, hyperbaric (1.5 atmospheres absolute), sedentary	≈ 3.2

water intake requirements increase to approximately 3.2 L/day (Greenleaf et al., 1977; Gunga et al., 1993). Cold exposure did not alter intake, but heat stress increased total daily water intake (Welch et al., 1958).

Limited data were available for women. Women are physically smaller, thus they probably have lower water requirements due to lower metabolic expenditures. A study of three Japanese women (likely smaller than average U.S. adult women) indicated a water intake requirement of approximately 1.6 L/day (Yokozawa et al., 1993).

Water Turnover

Water turnover studies have been conducted to evaluate water needs and assume a balance between influx and efflux (Nagy and Costa, 1980). Rates of body water turnover can be determined by administering a drink with deuterium (D_2O) or tritium (^3H_2O) labeled water and then following the decline (or disappearance) in hydrogen isotope activity over time. The isotope activity declines because of loss of the labeled water via excretion, evaporation, and dilution from intake of unlabeled water. If proper procedures are employed, these measurements will yield values within 10 percent or less of actual water flux (Nagy and Costa, 1980).

Figure 4-7 provides data on the daily water turnover for infants and children (Fusch et al., 1993). Water turnover (when expressed

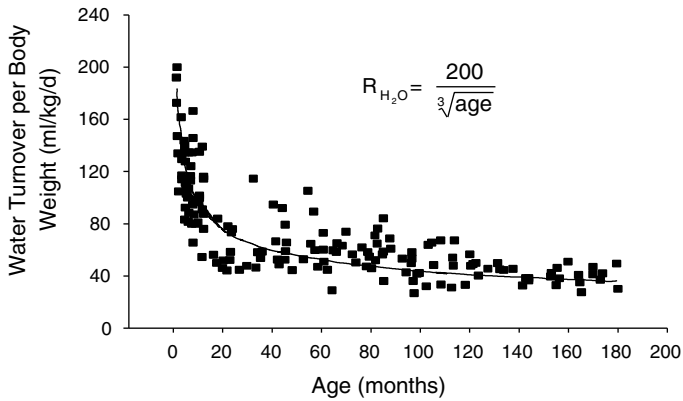

FIGURE 4-7 Daily water turnover per kg of body weight in infants and children. Reprinted with permission, from Fusch et al. (1993). Copyright 1993 by Springer-Verlag.

per kg of body weight) is highest during the first weeks of life and declines by some 40 percent during infancy. It declines further, but at a slower pace during childhood and adolescence. In a German study, mean water turnover at ages 1 to 3 months was 160 mL/kg/day, compared with 97 mL/kg/day at ages 10 to 12 months, and 40 mL/kg/day at ages 13 to 15 years (Fusch et al., 1993). Daily fluid intake in bottle-fed infants was compared over a 15-day study period using two methods to determine intake (Vio et al., 1986). Water turnover as measured by deuterium tracer was compared with directly measured fluid intake. Daily fluid intakes of 0.71 L/day (153 mL/kg/day) and 0.70 L/day (151 mL/kg/day) were reported for the direct and water turnover methodology ($r = 0.98$), respectively. Other studies have found close agreement (Butte et al., 1988) or slightly higher (Butte et al., 1991) values for water turnover versus direct measurement of daily fluid intake in infants.

Table 4-6 provides studies examining daily water turnover for adults in a variety of conditions. These values are generally higher than in water balance studies because subjects are often more active and exposed to outside environments. Daily water turnover rates were approximately 3.2 L and 4.5 L for sedentary and active men, respectively. Several studies found daily water turnover rates greater than 5 L; presumably these were more active persons who may have encountered heat stress. Women generally had approximately 0.5 to 1.0 L/day lower daily water turnover rates than their male counterparts.

Water turnover was measured in 458 noninstitutionalized adults (ranging from 40 to 79 years of age) who lived in temperate climates (Raman et al., 2004). Daily turnover averaged 3.6 and 3.0 L in men and women, respectively. The water turnover values were corrected for metabolic water and water absorption from humidity to provide preformed water values. The preformed water values averaged 3.0 L/day (range 1.4 to 7.7 L/day) for men and 2.5 L/day (range 1.2 to 4.6 L/day) for women. The lower values in women were not accounted for by differences in body size.

METHODS FOR ESTIMATING HYDRATION STATUS

Total Body Water Changes

Total body water (TBW) is accurately determined by dilution of a variety of indicators. Repeated measurements are required to assess total body water changes. The technical requirements and cost for

TABLE 4-6 Summary of Daily Water Turnover Studies on Adults

Reference	Subjects	Conditions	Water Turnover (L/d)
Schloerb et al., 1950	17 men 11 women	Not reported	3.4 men 2.3 women
Fusch et al., 1996	11 men, 2 women	Before and after high-altitude trek of 4,900 to 7,600 m	3.3 before (combined) 5.5 after (combined)
Leiper et al., 1996	6 men (sedentary) 6 men (active)	Temperate	3.3 (sedentary < 60 min exercise/d) 4.7 (active)
Lane et al., 1997	13 male astronauts	Ground-based period	3.8
Blanc et al., 1998	8 men	Sedentary Head-down bed-rest	3.5 3.2
Fusch et al., 1998	11 men 4 women	Temperate	5.7 (combined)
Leiper et al., 2001	6 men (sedentary) 6 men (active)	Temperate	2.3 (sedentary) 3.5 (active)
Ruby et al., 2002	8 men 9 women	Arduous wildfire suppression activity	7.3 men 6.7 women
Raman et al., 2004	66 men (40–49 yr) 58 men (50–59 yr) 56 men (60–69 yr) 49 women (40–49 yr) 48 women (50–59 yr) 36 women (60–69 yr)	Temperate	3.8 (free living) 3.6 3.6 3.3 3.0 2.9

repeated measurements with dilution methods make them impractical for routine assessment of TBW changes. Bioelectric impedance analysis (BIA) has recently gained attention because it is simple to use and allows rapid, inexpensive, and noninvasive estimates of TBW. Absolute values derived from this technique correlate well with TBW values obtained by isotope dilution (Kushner and Schoeller, 1986; Kushner et al., 1992; Van Loan et al., 1995). These valida-

tion studies were performed on euhydrated subjects under standardized clinical conditions (e.g., controlled diet, body posture, skin temperature, inactivity).

Studies have indicated that BIA may not have sufficient accuracy to validly detect moderate dehydration (approximately 7 percent TBW) and loses resolution with isotonic fluid loss (O'Brien et al., 1999). Because fluid, electrolyte, and plasma protein concentrations can have independent effects, BIA can provide misleading values regarding dehydration or hyperhydration status (Gudivaka et al., 1999; O'Brien et al., 2002). Fluid and electrolyte concentrations may have independent effects on the BIA signal, thus often providing grossly misleading values regarding dehydration status (O'Brien et al., 2002). The BIA with a $0/\infty$ – kHz parallel (Cole-Cole) multifrequency model may have promise to measure body hydration changes if corrections are made for changes in plasma protein concentration (Gudivaka et al., 1999). However, recently a multifrequency BIA with Cole-Cole analysis was reported not to be sensitive to hypertonic dehydration (Bartok et al., 2004).

Plasma and Serum Osmolality

Plasma osmolality provides a marker of dehydration levels. Osmolality is closely controlled by homeostatic systems and is the primary physiological signal used to regulate water balance (by hypothalamic and posterior pituitary arginine vasopressin secretion), resulting in changes in urine output and fluid consumption (Andreoli et al., 2000; Knepper et al., 2000). Plasma osmolality rarely varies beyond ± 2 percent and is controlled around a set-point of 280 to 290 mOsmol/kg; this set-point increases with aging and becomes more variable among people. Water deprivation (if it exceeds solute losses) increases the osmolality of plasma and of the ECF and thus fluids bathing the hypothalamus. This causes loss of ICF from osmoreceptor neurons, which then signals the release of arginine vasopressin from the hypothalamus and the posterior pituitary. Arginine vasopressin acts on the renal tubules to increase water reabsorption.

Arginine vasopressin release is proportional to increased plasma osmolality and decreased plasma volume. While body water loss will induce plasma volume reduction and increased plasma osmolality, the influence of body water loss on each depends upon the method of dehydration, physical fitness level, and heat acclimatization status (Sawka, 1988; Sawka and Coyle, 1999).

Many studies have measured plasma osmolality of euhydrated sub-

TABLE 4-7 Plasma Osmolality for Euhydrated Subjects in Carefully Controlled Fluid Balance Studies

Reference	Subjects Mean age ± S.D.[a]	Plasma Osmolality (mOsmol/kg)
Sawka et al., 1983a	Men, 25 ± 4 yr	284
Sawka et al., 1983b	Men, 24 ± 3 yr Women, 26 ± 3 yr	281
Sawka et al., 1984a	Men, 24 ± 3 yr Women, 26 ± 3 yr	281
Fish et al., 1985	Men and women, 20–37 yr	281
	Men and women, 62–88 yr	291
Sawka et al., 1988	Men, 33 ± 3 yr	283
Mack et al., 1994	Men, 18–28 yr	281
	Men, 65–78 yr	287
Freund et al., 1995	Men, 24 ± 2 yr	287
Montain et al., 1995	Men, 24 ± 6 yr	281
Stachenfeld et al., 1996	Men and women, 24–33 yr	282
	Men and women, 67–76 yr	286
Latzka et al., 1997	Men, 19–36 yr	282
Montain et al., 1997	Men, 24 ± 6 yr	281
Stachenfeld et al., 1997	Men and women, 20–28 yr	285
	Men and women, 65–76 yr	288
Latzka et al., 1998	Men, 19–36 yr	283
O'Brien et al., 1998	Men, 24 ± 2 yr	280
Noakes et al., 2001	Men, 28–44 yr	279
Popowski et al., 2001	Men, 23 ± 3 yr	288

[a] S.D. ± stardard deviation.

jects in controlled fluid balance studies. Table 4-7 provides results from some of these studies. Note that plasma osmolality ranged from 279 to 291 mOsmol/kg and averaged approximately 284 mOsmol/kg, with slightly higher values for older populations. Elderly persons had approximately 3 to 6 mOsmol/kg higher plasma osmolality than the young adults studied (Mack et al., 1994; Stachenfeld et al., 1996, 1997).

Figure 4-8 provides a compilation of 19 studies (181 subjects) where plasma osmolality was measured at several hydration levels. TBW was either directly measured or calculated based upon body composition information. A strong negative relationship ($p < 0.0001$) ($r = -0.76$) was found between TBW changes and plasma osmolality changes. Similar relationships have been reported based on smaller sample sizes of individual data (Sawka et al., 2001; Senay and Christensen,

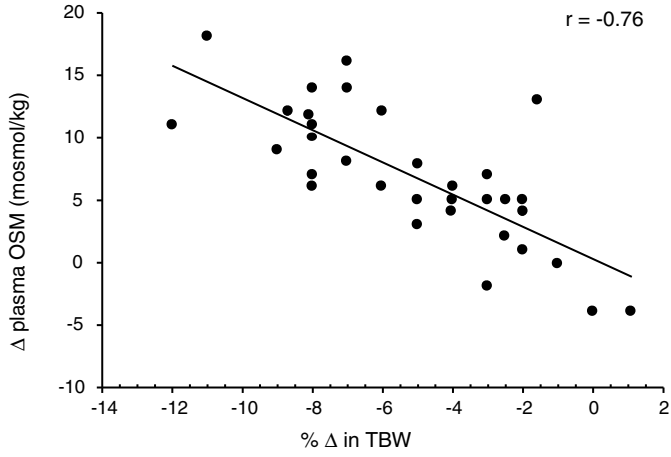

FIGURE 4-8 Relationship of change in plasma osmolality to change in total body water from 19 studies representing 181 subjects (Armstrong et al., 1985, 1997; Cheung and McLellan, 1998; Gonzalez-Alonso et al., 1997; Maresh et al., 2001; Maughan et al., 1996; Miescher and Fortney, 1989; Montain and Coyle, 1992; Montain et al., 1995; Neufer et al., 1989a, 1991; Noakes et al., 2001; O'Brien et al., 1998; Sawka et al., 1983b, 1985, 1988, 1989a, 1989b, 1992). The data points represent mean data reported in these studies. $y = 0.2943 - 1.2882x$; $p = < 0.0001$.

1965). Clearly, plasma osmolality provides a good marker for dehydration status if water loss is greater than solute loss. When solute and water are lost proportionately, such as with diarrhea or vomiting, osmolality remains constant and vasopressin release is blunted. However, the resulting ECF loss will stimulate the renin-angiotensin-aldosterone system as a means to increase sodium and hence water retention (Share et al., 1972). This mechanism appears to be less robust in elderly individuals (Dontas et al., 1972).

Table 4-8 provides the serum osmolality for selected deciles of total water intake by gender in the Third National Health and Nutrition Examination Survey (NHANES III). A more complete presentation of NHANES III data can be found in Appendix Table G-1. Serum osmolality concentrations were essentially identical (maximum range 3 mOsmol/kg) for the lowest (1st), middle (5th), and highest (10th) deciles within each age group. These data indicate that persons in the lowest and highest deciles of *total* water intake were not systematically dehydrated or hyperhydrated. In agreement

TABLE 4-8 Serum Osmolality Concentration for Selected Deciles of Daily Total Water Intake in Men and Women

		Men		Women	
Age	Decile of Total Water Intake	Total Water Intake, L/d (mean)	Mean Serum Osmolality (mOsmol/kg)	Mean Total Water Intake (L/d)	Mean Serum Osmolality (mOsmol/kg)
12–18 yr	1st	1.36	278	0.94	278
	5th	2.79	279	2.20	276
	10th	6.46	281	5.52	277
19–50 yr	1st	1.69	279	1.25	277
	5th	3.31	280	2.61	277
	10th	7.93	280	6.16	277
51–70 yr	1st	1.64	280	1.32	281
	5th	3.17	283	2.68	281
	10th	7.20	281	5.81	279
71+ yr	1st	1.44	283	1.19	282
	5th	2.71	283	2.38	283
	10th	5.45	281	4.85	282

SOURCE: Third National Health and Nutrition Examination Survey, Appendix Table G-1.

with Table 4-8, the oldest persons (greater than 70 years of age) had slightly higher serum osmolality levels. The serum osmolality concentrations observed in NHANES III (Table 4-8) were slightly lower for all age groups than the plasma osmolality levels from the balance studies previously described (Table 4-7). In general, serum and plasma osmolality values are usually nearly identical; however, several handling and analytical factors can cause small differences between them (Tietz, 1995).

Plasma Sodium Concentration

Sodium is the primary cation of the ECF. Any loss of water in greater proportion than electrolyte losses will increase sodium concentrations in ECF compartments. Figure 4-9 provides a compilation of four studies (32 subjects) where plasma sodium concentration was measured at several hydration levels. TBW was either directly measured or calculated based upon body composition information. A moderate negative relationship ($r = -0.46$) was obtained between the decrease in TBW and increase in plasma sodium levels ($p = 0.14$). If data are analyzed for only the studies that

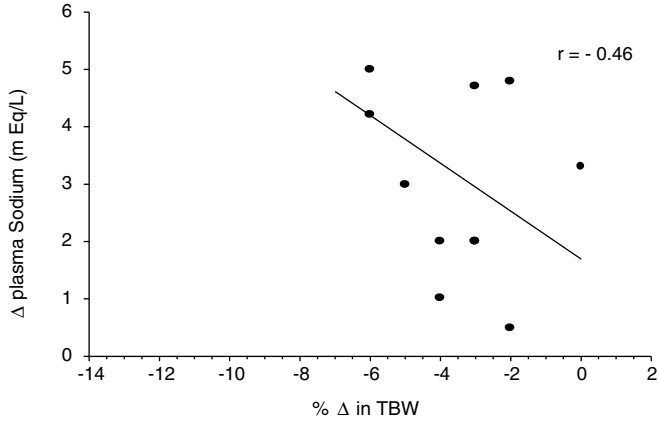

FIGURE 4-9 Relationship of change in plasma sodium to change in total body water from 4 studies representing 32 subjects (Fallowfield et al., 1996; Maughan et al., 1996; McConell et al., 1999; Montain et al., 1995). The data points represent mean data reported in these studies. y = 1.6927 – 0.4175x; $p = 0.14$.

presented both osmolality (Figure 4-9) and sodium data, then negative correlations of $r = -0.82$ and $r = -0.28$ were found between decreases in TBW and increases in osmolality and sodium levels, respectively. A negative relationship of $r = -0.71$ and $r = -0.57$ (based on 22 experiments) has been reported between decreases in TBW (as measured by body weight changes) and increases in plasma osmolality and plasma sodium levels, respectively (Senay and Christensen, 1965). Based on this data, plasma sodium changes are not as strongly related to changes in body hydration status as plasma osmolality changes.

Analysis of the data on plasma osmolality and sodium concentrations measured in nine heat acclimated subjects when euhydrated and after thermal dehydration by 3 and 5 percent of their weight indicated strong negative relationships between a decrease in total body water and (1) an increase in osmolality ($r = -0.92$), and (2) an increase in sodium ($r = -0.90$) (Montain et al., 1997). Further analysis indicated a relationship ($r = 0.56$) between the increases in sodium and in osmolality. Figure 4-10 depicts these data; note that the magnitude of increased plasma sodium concentration is markedly less than the increase in plasma osmolality. Therefore, the smaller increase in sodium concentration for a given water deficit may result in a smaller range for interstudy analyses and lead to

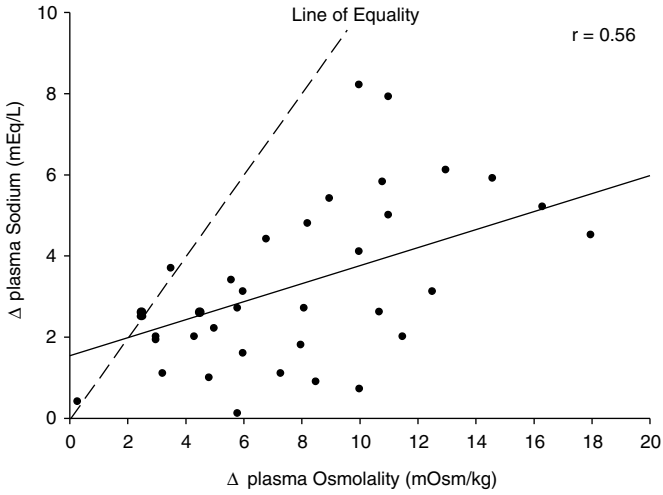

FIGURE 4-10 Relationship of change in plasma osmolality and plasma sodium concentration changes from thermal dehydration. Data from Montain et al. (1997). y = 0.2218x + 1.5461, $p = 0.0002$.

weaker relationships between change in plasma sodium and change in hydration status.

Plasma Volume Changes

Hyperhydration induces a modest increase in plasma volume (Freund et al., 1995; Latzka et al., 1997). Dehydration will decrease plasma volume, but the magnitude of reduction is variable. For example, heat acclimatized persons have a smaller plasma volume reduction for a given body water deficit than do unacclimatized persons (Sawka et al., 1988). By virtue of having a more dilute sweat, heat acclimatized persons have additional solutes remaining within the extracellular space to exert an osmotic pressure and redistribute fluid from the intracellular space. If an individual dehydrates from diuretic medication, a much greater ratio of plasma loss to total body water loss occurs compared with exercise-heat induced dehydration (O'Brien et al., 1998).

Figure 4-11 provides a compilation of 16 studies (146 subjects) where plasma volume was measured at several hydration levels. TBW was either directly measured or calculated based upon body composition information. A moderate correlation ($r = 0.56$) was observed

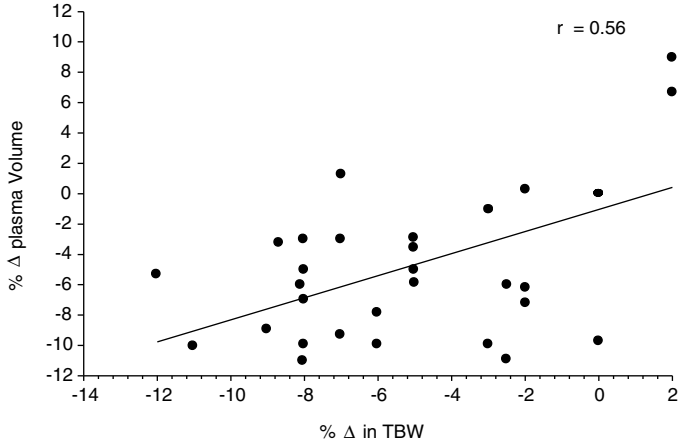

FIGURE 4-11 Relationship of change in plasma volume to change in total body water from 16 studies representing 146 subjects (Armstrong et al., 1985; Cheung and McLellan, 1998; Fallowfield et al., 1996; Gonzalez-Alonso et al., 1997; Kristal-Boneh et al., 1988; McConell et al., 1999; Miescher and Fortney, 1989; Montain and Coyle, 1992; Montain et al., 1995; O'Brien et al., 1998; Sawka et al., 1983b, 1985, 1988, 1989a, 1989b, 1992). The data points represent mean data reported in these studies. $y = -1.0466 + 0.7270x$, $p = 0.0004$.

between change in TBW and change in plasma volume. A strong relationship ($r = 0.70$) between plasma volume reduction and TBW reduction was seen in individual data on heat acclimatized subjects (Sawka et al., 2001). However, since subject status (e.g., heat acclimatization and perhaps physical fitness) and method of dehydration modifies the plasma volume reduction for a given dehydration level (Sawka, 1992), it is probably not a good index of hydration for all populations.

Blood Urea Nitrogen

Although blood urea nitrogen (BUN) is primarily considered an indicator of kidney function, it is also used as an indicator of dehydration in clinical settings. The pattern of high BUN (normal range 8 to 25 mg/dL) and otherwise normal renal function (e.g., normal creatinine or creatinine clearance) is considered an indicator of hypovolemia (a reduction in plasma or blood volume). However, BUN is also directly related to protein intake. Therefore, while BUN

can be an indicator of hydration status, other biochemical values must be considered in order to assess hydration status versus kidney function.

An elevated BUN:creatinine ratio (greater than 25) was seen in 2 of 37 elderly, long-term care patients who experienced no febrile episodes and no documentation of impaired oral intake (Weinberg et al., 1994a). The BUN:creatinine ratio remained relatively constant over a 6-month period in stable male residents (Weinberg et al., 1994b). Still, although the BUN:creatinine ratio, like BUN itself, has been used to assess hydration status, lack of specificity hinders its use as a measure of hydration status.

Urine Indicators

Volume and Color

Urine volume is often used as an indicator of hydration status. If healthy individuals have urine outputs of approximately 100 mL/hour, they are probably well hydrated (see Figure 4-4). Higher urine outputs (300 to 600 mL/hour) are probably indicative of fluid excess (Freund et al., 1995; Lee, 1964). If urine output falls to less than 30 mL/hour for extended periods with an average diet, the person is probably dehydrated (see Figure 4-4).

The color of urine darkens or lightens with low or high output levels (because the solute load is either concentrated or diluted, respectively). Thus urine color has been used as an indicator of hydration status (Wakefield et al., 2002). However, no precise relationship between urine color and hydration level exists. Furthermore, diet, medications, and vitamin use can affect urine color. Nonetheless, urine color can provide a good educational tool for dehydration or overhydration (Casa et al., 2000). A urine color chart for athletes to teach them about proper hydration is available (Casa et al., 2000). Although not nearly as precise as biochemical measures, urine color can give a crude indication of hydration status.

Urine Specific Gravity and Urine Osmolality

Because urine becomes more concentrated with dehydration, both urine specific gravity and urine osmolality have been used as indicators of hydration status. Urine specific gravity and urine osmolality increase with dehydration and are strongly correlated (r = 0.82–0.97) with each other (Armstrong et al., 1994; Popowski et al., 2001). It should be noted that the validity of the urine specific gravity and

urine osmolality as indices in assessing hydration status is improved when the first morning urine, rather than a random collection, is used due to a more uniform volume and concentration (Sanford and Wells, 1962; Shirreffs and Maughan, 1998). Many studies have used these urine indices to access fluid balance and found poor (Armstrong et al., 1994; Francesconi et al., 1987; Hackney et al., 1995; O'Brien et al., 1996) or moderate (Adolph, 1947b; Shirreffs and Maughn, 1998) relationships with different indicators of dehydration status. For example, nonsignificant relationships between plasma osmolality with urine specific gravity ($r = 0.46$) and with urine osmolality ($r = 0.43$) were found in a well-controlled study of thermally dehydrated subjects (Popowski et al., 2001).

For "normally" hydrated (euhydrated) persons, urine specific gravity values range from 1.010 to 1.030 (Armstrong et al., 1994; Popowski et al., 2001; Sanford and Wells, 1962; Zambraski et al., 1974). It has generally been accepted that a urine specific gravity of less than or equal to 1.02 represents euhydration (Armstrong et al., 1994; Popowski et al., 2001), and a urine specific gravity greater than 1.03 represents dehydration (Armstrong et al., 1994; Francesconi et al., 1987; Popowski et al., 2001). Adolph (1947b) published individual data regarding urine specific gravity at different levels of water deficit (Figure 4-12). Urine specific gravity increases with water deficit; however, considerable individual variability exists. Although a urine specific gravity greater than 1.03 indicates probable dehydration, the magnitude of the water deficit cannot be determined.

Normal values for urine osmolality vary from 50 to 1,200 mOsmol/L (Tilkian et al., 1995). Therefore, in the setting of such variability, there may be no single threshold for urine osmolality and hydration status. However, individual increases in urine osmolality can provide an approximation of a person's water deficit, assuming the solute load remains constant (Armstrong et al., 1994; Shirreffs and Maughan, 1998). In addition, urine osmolality is increased when osmotically active solutes are excreted, such as glucose in patients with uncontrolled diabetes mellitus (Tilkian et al., 1995). For these reasons (i.e., high variability and its dependence on solute excretion), urine osmolality is not considered a good indicator of hydration status.

Saliva Specific Gravity

Saliva specific gravity is slightly higher than water (Shannon and Segreto, 1968). Several studies have examined dehydration and sali-

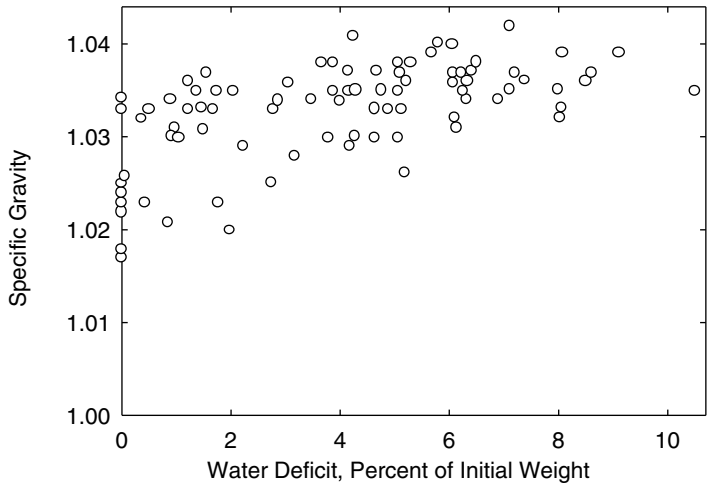

FIGURE 4-12 Individual urine specific gravity values at a range of water deficit levels.
SOURCE: Adolph (1947b). Reprinted with permission from the Papers of Edward Adolph collection at the Edward G. Miner Library, University of Rochester Medical Center.

vary specific gravity. Salivary flow was shown to decrease after a water deficit exceeding 2 percent of body weight, but there was considerable variability in response (Adolph and Wills, 1947). Significant decreases in saliva flow rate were found during dehydration of 2 to 3 percent body weight using 24-hour water deprivation studies (Ship and Fischer, 1997, 1999). One study determined that salivary osmolality increases during exercise in the heat accompanied by modest (2.9 percent body weight loss) dehydration (Walsh et al., 2004).

Body Weight Changes

Body weight changes are frequently used to estimate sweating rates and therefore changes in total body water (e.g., Gosselin, 1947). This approach is usually used to estimate changes over a relatively short duration when food and fluid intakes and excretions are carefully controlled. The validity of this estimate depends upon body weight measurements not being confounded by other nonfluid factors that can influence body weight changes. If proper controls are made, body weight changes can provide a more sensi-

tive estimate of total body water changes than repeat measurements by dilution methods (Gudivaka et al., 1999).

Potential confounding effects of urine loss, fluid intake, respiratory water loss, metabolic mass loss, water trapped perspiration in clothing on sweat loss, and therefore total body water change estimates for individuals performing exercise in hot and cool conditions have been examined (Cheuvront et al., 2002). Significant errors in estimating sweating rate are introduced unless nonperspiration fluid losses are factored into the body weight changes (Cheuvront et al., 2002). Likewise, carbohydrate loading in athletes will result in elevated baseline body weights that do not reflect euhydration, as the muscle glycogen will osmotically hold water. Overall, body weight changes provide an effective index of body water changes if other factors influencing body weight are carefully controlled.

Thirst

Thirst is "the desire to drink by both physiological and behavioral cues, resulting from deficit of water" (Greenleaf, 1992), through which people replenish their fluid losses during short-term periods (several hours) (Adolph and Wills, 1947; Eichna et al., 1945). Various scales have been developed over the years to quantify thirst by rating the sensation of, for example, dry mouth or dry throat. However, the most practical and commonly used approach in animal and human studies has been to document the volume of *ad libitum* (voluntary) drinking as a surrogate measurement of thirst. Despite *ad libitum* drinking, humans tend to under-replace their fluid needs over the short term (Johnson, 1964).

Triggering of thirst occurs through perceptual and physiological mechanisms (Fitzsimons, 1976; Greenleaf and Morimoto, 1996; Rolls and Rolls, 1982). For example, increases in plasma osmolality, plasma volume reduction, and several thirst sensations all made substantial contributions to predicting *ad libitum* fluid replacement following water deficits of 3, 5, and 7 percent of body weight loss (Engell et al., 1987).

Perceptual Factors

Voluntary drinking of a beverage is affected by its palatability, which is determined by its color, flavor, odor, and temperature (Boulze et al., 1983; Hubbard et al., 1984; Meyer et al., 1994; Szlyk et al., 1989; Wilk and Bar-Or, 1996; Zellner et al., 1991). These factors

are greatly influenced by cultural preferences; therefore, broad generalizations are difficult. In a study on the effect of water temperature on voluntary drinking, dehydrated men drank the highest amounts when the water temperature was 15°C (59°F). Higher and lower temperatures resulted in a smaller drinking volume, even though the cooler drinks were rated more "pleasurable" (Boulze et al., 1983). In another study, water at 15°C (59°F) was consumed at greater volumes than water at 40°C (104°F) (Szlyk et al., 1989). When children were exposed to 3 hours of intermittent exercise at 35°C (95°F) and 45 to 50 percent relative humidity, their *ad libitum* consumption of flavored water was 45 percent greater than with unflavored water (Figure 4-13) (Wilk and Bar-Or, 1996). Likewise, adults who performed desert-simulated walks at 40°C (104°F) drank approximately 50 percent more flavored water than unflavored water (Hubbard et al., 1984).

The sweetness of a drink is a major factor in its palatability, but people differ in their preferred flavor. Flavor preference depends on various factors, including ethnic and cultural backgrounds. For example, in one study with Canadian children, most preferred grape to orange or apple flavors and drank more when presented with a

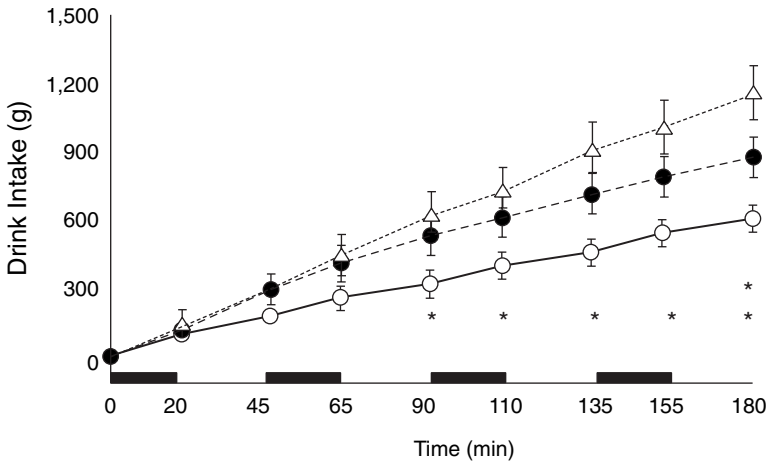

FIGURE 4-13 Cumulative voluntary drink intake of unflavored water (open circles), flavored water (black circles), and flavored sodium chloride (18 mmol/L) plus carbohydrate (6 percent) solution (triangles). Twelve 9- to 12-year-old boys cycled intermittently (black bars) at 35°C, 45 to 50% relative humidity. Reprinted with permission, from Wilk and Bar-Or (1996). Copyright 1996 by the American Physiological Society.

grape-flavored beverage (Meyer et al., 1994). In contrast, children in Puerto Rico had no preference for any single flavor (Rivera-Brown et al., 1999).

Physiological Triggers

Based on studies of various animal species, including humans, there seems to be three main physiological triggers for thirst: cerebral osmoreceptors, extra-cerebral osmoreceptors, and volume receptors (Fitzsimons, 1976; Greenleaf, 1992; Greenleaf and Morimoto, 1996). The osmoreceptors respond to cellular dehydration, which occurs when fluids leave the cells as a result of osmotic forces. The volume receptors respond to extracellular dehydration that results from loss of fluid from the vascular and interstitial spaces. While the osmoreceptors respond to small increases in osmolality, the volume receptors are activated by more drastic fluid losses. The osmoreceptors, therefore, are considered the first line of homeostatic defense against dehydration.

The location of these cells varies among species, but they are concentrated mostly in the hypothalamic area of the brain. Stimulation of the osmoreceptors activates drinking behavior and the release of arginine vasopressin hormone. The latter increases water permeability of the collecting tubules and thereby reduces free water loss and urine volume. There is evidence that either sodium chloride or an increase in osmolality (probably through separate cells) can activate the cerebral osmoreceptors, but it is assumed that the increase in osmotic forces is the more important stimulus (Greenleaf and Morimoto, 1996). The addition of 18 mmol/L of sodium chloride to flavored water triggered an increase of 31 percent in *ad libitum* drinking of children who exercised in the heat, compared with flavored water alone (Wilk and Bar-Or, 1996). Similar responses have been described for animals (Okuno et al., 1988) and adult humans (Nose et al., 1988).

Other osmoreceptors located in the oropharynx, gastrointestinal tract, and particularly the liver-portal system respond to drinking and modulate the thirst drive. Their existence has been postulated through experiments in which thirst and arginine vasopressin levels were modulated soon after drinking (or after injection of fluid to the liver portal system), before there were any changes in plasma osmolality or volume.

Thirst may be triggered by a decrease in blood volume, such as in hemorrhage or severe dehydration. This occurs through volume or stretch receptors that are sensitive to a drop in pressure at sites such

as the large systemic veins and the right atrium. These receptors, through the vagal system, stimulate thirst and drinking. Because of the compensatory activation of the renin-angiotensin-aldosterone system, preservation of body fluid is also achieved through a reduction in urinary output. Triggering of thirst through hypovolemia requires more than small changes in blood volume. The role of various thirst mechanisms with altered hydration status has been reviewed in detail elsewhere (Mack and Nadel, 1996; Stricker and Sved, 2000). However, in almost all situations where smaller volumes are lost over time (such as 2 to 3 L of sweat over 6 hours due to high temperatures or exercise), thirst mechanisms come into play over the ensuing 24 hours to trigger replacement of fluids lost; thus, in general, normal hydration is maintained by thirst mechanisms and normal drinking behavior. Such replacement is enhanced by consuming beverages at meals and in other social situations (Engell, 1995; Szlyk et al., 1990), which may be a necessary component to achieve adequate rehydration within a short period of time due to minor fluid deficits induced by exercise or heat strain.

Dehydration, Health, and Performance

Well-Being and Cognition

Dehydration can adversely influence cognitive function and motor control. Dehydration and poor mental function have been reported to be associated in physically ill older people (Seymour et al., 1980). Table 4-9 summarizes studies that examined the effects of dehydration on cognitive performance and motor function in healthy individuals.

Interpretation of these reports is difficult because the experimental designs often do not allow discrimination of confounding factors, such as effect of thermal (or exercise) stress and that of dehydration *per se* (Epstein et al., 1980; Hancock, 1981; Leibowitz et al., 1972; Sharma et al., 1983). For example, a degradation in mental alertness, associative learning, visual perception, and reasoning ability were noted when healthy men exercised while exposed to a high climatic heat stress (Sharma et al., 1983). Although the subjects drank water *ad libitum*, they may not have consumed enough fluids over the 4-hour session and thus became dehydrated due to the exercise and heat stress. However, the possible effect of dehydration on the above mental functions was not addressed. In another study, men and women exercised in the heat for 6 hours to elicit dehydration levels of 2.5 and 5 percent (Leibowitz et al., 1972).

TABLE 4-9 Cognitive and Motor Control Functions Reported to Be Affected by Dehydration

Function	Reference	Subjects	Conditions	Results
Perception of fatigue	Cian et al., 2000	8 men	2.8% dehydration by exercise or climatic heat	Increased rating of fatigue
Rating of mood	Cian et al., 2000	8 men	2.8% dehydration by exercise or climatic heat	No effect on mood
Target shooting	Epstein et al., 1980	9 men	2.5% dehydration by climatic heat	Reduced speed and accuracy and increase in physiologic strain
Perceived discrimination	Cian et al., 2000	8 men	2.8% dehydration by exercise or climatic heat	Discrimination impaired
Choice reaction time	Leibowitz et al., 1972	4 men, 4 women	6-h exercise in the heat, causing 2.5% or 5% dehydration	Faster response time to peripheral visual stimuli, no effect on response time to central visual stimuli
	Cian et al., 2000	8 men	2.8% dehydration by exercise or climatic heat	No effect on response time
Visual-motor tracking	Gopinathan et al., 1988	11 men	1, 2, 3, or 4% dehydration, induced by exercise in the heat	Tracking impaired at 2% or more dehydration
Short-term memory	Cian et al., 2000	8 men	2.8% dehydration by exercise or climatic heat	Short-term memory impaired
	Gopinathan et al., 1988	11 men	1, 2, 3, or 4% dehydration, induced by exercise in the heat	Short-term memory impaired at 2% or more dehydration

TABLE 4-9 Continued

Function	Reference	Subjects	Conditions	Results
Long-term memory	Cian et al., 2000	8 men	2.8% dehydration by exercise or climatic heat	Impaired recall, especially following exercise
Attention	Gopinathan et al., 1988	11 men	1, 2, 3, or 4% dehydration, induced by exercise in the heat	Attention impaired at 2% or more dehydration
Arithmetic efficiency	Gopinathan et al., 1988	11 men	1, 2, 3, or 4% dehydration, induced by exercise in the heat	Arithmetic ability impaired at 2% or more dehydration

There was no difference in reaction time in response to central visual cues, but reaction time decreased when the visual cues were given at the periphery of the field of vision during the two dehydration conditions. Once again, interpretation of this finding is difficult because factors such as climatic heat stress, exercise-related fatigue, and boredom were not removed.

In a well-designed study, the arithmetic ability, short-term memory, and visual-motor tracking of 11 men who, on separate days, had water deficits of either 1, 2, 3, or 4 percent of body weight via thermal dehydration were assessed (Gopinathan et al., 1988). The subjects had ample rest in a temperate environment once they reached the target dehydration. This design allowed the researchers to observe the effects of dehydration *per se*, without fatigue or heat stress. This study revealed that a threshold level of 2 percent dehydration is required for deterioration of mental functions. A similar threshold was reported by other investigators (Sharma et al., 1986).

The adverse effects on mental function occurred irrespective of whether dehydration was achieved through exposure to the heat or as a result of exercise (Cian et al., 2001). A previous study by the same group suggested that exercise-induced dehydration was accompanied by a greater reduction in long-term memory (Cian et al., 2000), but the decrement in other functions was similar despite the mode of dehydration.

In conclusion, there is evidence to suggest that water deficits of 2 percent of body weight or more are accompanied by declining men-

tal function (Epstein et al., 1980). The mechanisms for this deficiency have not been elucidated.

Physical Work

Body water deficits can adversely influence aerobic exercise tasks (Sawka, 1992; Sawka and Coyle, 1999). The critical water deficit and

TABLE 4-10 Dehydration Effects on Maximal Aerobic Power and Physical Work Capacity

Study	Subjects	Environment[a]	Dehydration Process
Buskirk et al., 1958	13 men	83°C (115°F)	Heat
Saltin, 1964	10 men	36–38.5°C (68–70.5°F)	Heat and exercise
Craig and Cummings, 1966	9 men	46°C (78°F)	Heat and exercise
Herbert and Ribisl, 1972	8 men	N/A	Fluid restriction
Houston et al., 1981	4 men	N/A	Fluid restriction
Caldwell et al., 1984	16 men	N/A	Exercise
	15 men	N/A	Diuretic
	16 men	80°C (112°F), 50% RH	Sauna
Pichan et al., 1988	25 men	39°C (71°F), 60% RH	Fluid restriction and exercise in sauna
Webster et al., 1990	7 men	N/A	Exercise in rubberized sweat suit
Sawka et al., 1992	17 men	49°C (81°F), 20% RH	Fluid restriction and exercise
Burge et al., 1993	8 men	N/A	Exercise and fluid restriction
Walsh et al., 1994	6 men	30°C (62°F), 60% RH	Fluid restriction
Below et al., 1995	8 men	31°C (63°F), 54% RH	Fluid restriction
Fallowfield et al., 1996	4 men, 4 women	N/A	Fluid restriction
Montain et al., 1998b	5 men, 5 women	40°C (72°F), 20% RH	Exercise and hot room

[a] N/A = not available, RH = relative humidity.
[b] TM = treadmill, CY = cycle ergometer.
[c] NC = no change.

magnitude of performance decrement are related to the environmental temperature, exercise task, and probably the subject's unique biological characteristics (physical fitness, acclimatization state, tolerance to dehydration). Table 4-10 presents a summary of investigations concerning the influence of dehydration on maximal aerobic power and physical work capacity (e.g., how much aerobic-type exercise could be completed under a given set of conditions) in adults.

% Δ Wt	Exercise Mode[b]	Baseline Maximum Power (L/min)	Δ Maximum Aerobic Power[c]	Physical Work
–5	TM		↓ (–0.22 L/min)	—
–4	CY	3.96	NC	↓ (33%)
–2	TM	≈ 3.8	↓ (10%)	↓ (22%)
–4	TM	≈ 3.8	↓ (27%)	↓ (48%)
–5	CY		—	↓ (17%)
–8	TM	4.3	NC	—
–3	CY	3.61	NC	↓ (7 Watts)
–4	CY	4.15	↓ (8%)	↓ (21 Watts)
–5	CY	4.25	↓ (4%)	↓ (23 Watts)
–1	CY		—	↓ (6%)
–2	CY			↓ (8%)
–3	CY			↓ (20%)
–5	TM	3.76	↓ (7%)	↓ (12%)
–8	TM		—	↓ (54%)
–5	Rowing	4.65	NC	↓ (5%)
–1.8	CY	2.9	NC	↓ (34%)
–2	CY		↓ (6.5%)	—
–2	TM		—	↓ (25%)
–4	Leg kick		—	↓ (15%) endurance

In a temperate climate, body water deficits of less than 3 percent of body weight did not reduce maximal aerobic power; however, in hot climates, water deficits of 2 percent resulted in large reductions. Physical work capacity was reduced by dehydration in almost all examined conditions, with a greater effect when heat stress was also present. The influence of factors such as a person's initial maximal aerobic power, training status, and heat acclimatization status on the magnitude of aerobic performance decrements from body water deficits has not been delineated. In a study of dehydration in children at 1 and 2 percent of body weight loss, a greater increase in core body temperature than would have been expected to be observed in adults exercising in hot weather was noted (Bar-Or et al., 1980). Therefore, children may have greater adverse performance effects from the same extent of dehydration during heat stress than do adults.

The effects of body water loss on endurance exercise performance in 13 endurance exercise studies have been reviewed (Cheuvront et al., 2003) (see Table 4-11). Based on these studies, dehydration appears to alter cardiovascular, thermoregulatory, central nervous system, and metabolic functions. One or more of these alterations will degrade endurance exercise performance when dehydration exceeds 2 percent of body weight. These performance decrements are accentuated by heat stress.

In summary, the literature indicates that dehydration can adversely influence aerobic and endurance-type exercise performance. The level of body water deficit needed to induce performance decrements probably approximates 2 percent body weight deficit; however, some individuals are probably more sensitive and others less sensitive to the amount of body water deficit on performance consequences. In addition, experimental evidence supports the concept that greater body water deficits result in a greater magnitude of performance decrements. Finally, it appears that heat stress increases these adverse performance consequences from body water deficits.

Body water deficits can adversely affect anaerobic exercise performance but do not appear to alter muscular strength. Table 4-12 lists a summary of investigations concerning the influence of dehydration on anaerobic exercise performance. Note that half of the studies reported reductions in anaerobic performance with considerable variability in the magnitude of performance reduction. Table 4-13 presents a summary of investigations examining the influence of dehydration on muscular strength. Most studies reported no effect of dehydration on muscular strength.

Thermoregulation (Fever and Hyperthermia of Exercise) and Heat Strain Tolerance

Fever is a regulated rise in body temperature and is a common response to inflammation, infection, and trauma (Blatteis, 1998; Leon, 2002). Dehydration will probably enhance the fever response and therefore has implications for management of clinical conditions. Rats dehydrated by a 24-hour water deprivation period exhibited a more severe fever than normally hydrated rats after being injected with bacterial endotoxin (Morimoto et al., 1986). Subsequent studies by other investigators have reproduced these findings in rats (Watanabe et al., 2000), as well as in rabbits (Richmond, 2001), and suggest the enhanced fever is due to angiotensin II secretion, which increases production of pyrogenic cytokines, such as interleukin-1.

However, studies in guinea pigs have reported that dehydration reduced the febrile response to bacterial endotoxin and suggest that the mechanism may be an antipyretic effect of central arginine vasopressin (Roth et al., 1992). Although there may be some species differences, it seems reasonable to conclude that dehydration may induce higher fevers. In support of this belief, febrile episodes have been found to be frequently associated with dehydration in nursing home residents (Weinberg et al., 1994a).

Dehydration and Heat Strain Tolerance

During exercise, unlike with a fever, an increase in body temperature does not represent a set-point change and is proportional to the metabolic rate (Sawka et al., 1996a). Dehydration increases core temperature responses during exercise in temperate and hot climates (Sawka and Coyle, 1999). A deficit of only 1 percent of body weight has been reported to elevate core temperature during exercise (Ekblom et al., 1970). Figure 4-14 summarizes results from studies that examined multiple dehydration levels within the same subjects during exercise. As the magnitude of water deficit increased, there was a concomitant graded elevation of core temperature. The magnitude of core temperature elevation ranged from 0.1°C to 0.23°C for every percent body weight lost (Brown, 1947a; Gisolfi and Copping, 1974; Greenleaf and Castle, 1971; Montain et al., 1998a; Sawka et al., 1985; Strydom and Holdsworth, 1968). The core temperature elevation from dehydration may be greater during exercise in hot compared with temperate climates. Dehydration not only elevates core temperature, but it negates many thermal

TABLE 4-11 Dehydration Effects on Endurance Exercise Performance

Reference	Sample Size[a]	Exercise[b]
Pitts et al., 1944	5 men	Walk 3.5 mph, 2.5% grade for 5 h
Brown, 1947a	13 men, NF 9 men, AL	21-mi desert hike
Ladell, 1955	4 men	Bench step to exhaustion
Maughan et al., 1989	6 men	CE 70% VO_{2max} to exhaustion
Barr et al., 1991	5 men 3 women	CE 55% VO_{2max} for 6 h (intermittent)
Walsh et al., 1994	6 men	CE 70% VO_{2max} for 60 min, then 90% VO_{2max} to exhaustion
Below et al., 1995	8 men	CE 50% VO_{2max} for 50 min, then PR
Robinson et al., 1995	8 men	CE PR (total work in 60 min)
Fallowfield et al., 1996	4 men 4 women	TM run at 70% VO_{2max} to exhaustion
McConell et al., 1997	7 men	CE 69% VO_{2max} for 120 min, then 90% VO_{2max} to exhaustion
Mudambo et al., 1997a	18 men, NF 6 men, SF	Walk/run/obstacle course (3 h)
McConell et al., 1999	8 men	CE 80% VO_{2max} for 45 min, then 15 min PR
Bachle et al., 2001	4 men 7 women	CE 60 min PR

[a] NF = no fluid, AL = *ad libitum*, SF = some fluid (> NF, < F), F = fluid ≥ sweat losses.

[b] CE = cycle ergometer, PR = performance ride or run, TM = treadmill, VO_{2max} = maximal oxygen uptake.

[c] RH = relative humidity.

[d] RPE = rating of perceived exertion, TTE = time to exhaustion.

SOURCE: Cheuvront et al. (2003). Reprinted with permission, from Cheuvront et al. (2003). Copyright 2003 by Current Science, Inc., Philadelphia, PA.

Environment[c]	Drink Conditions	Dehydration (% body weight)	Performance Results[d]
35°C, 83% RH	NF, AL, F	No data	NF = ↓ (~60%) in walk duration; ↑ RPE vs. AL and F
31–39°C	NF, AL	NF = 6.3 AL = 4.5	NF = 7 of 13 failed to complete hike (54%) AL = 3 of 9 failed to complete hike (33%)
38°C, 78% RH 38°C, 30% RH	NF, F	No data	NF = ↓ (25%) in work tolerance time vs. F NF = ↓ (~20%) in walk duration; ↑ RPE vs. AL and F
Laboratory	NF, SF	NF = 1.8 SF = 2.0	No differences in TTE between NF and SF
30°C, 50% RH	NF, SF	NF = 6.4 F = 1.2	NF = ↓ (25%) in TTE and ↑ RPE vs. SF
30°C, 60% RH	NF, F	NF = 1.8 F = 0.0	NF = ↓ (31%) in TTE and ↑ in RPE vs. F
31°C, 54% RH	NF, F	NF = 2.0 F = 0.5	NF = ↓ (7%) in performance vs. F
20°C, 60% RH	NF, F	NF = 2.3 F = 0.9	NF = ↑ (1.7%) in PR vs. F
20°C	NF, SF	NF = 2.0 SF = 2.7	NF = ↓ (25%) in TTE vs. SF
21°C, 43% RH	NF, SF, F	NF = 3.2 SF = 1.8 F = 0.1	NF = ↓ (48%) in PR vs. F only
39°C, 28% RH	NF, SF	NF = 7 SF = 2.8	NF = 6/18 subjects failed to complete 3-h exercise bout vs. SF NF = ↑ in RPE vs. SF
21°C, 41% RH	NF, SF, F	NF = 1.9 SF = 1.0 F = 0.0	No differences in PR among trials
21°C, 72% RH	NF, F	NF = 1.0 F = ↑ 0.5	No differences in PR or RPE among trials

TABLE 4-12 Dehydration Effects on Anaerobic Performance

Reference	Subjects	Dehydration Process[a]	% Δ Wt	Anaerobic Method	Result[b]
Jacobs, 1980	11 men	Heat	–5	Wingate Anaerobic Test	NC
Houston et al., 1981	4 men	Fluid restriction	–8	Supramaximal run	NC
Nielsen et al., 1981	6 men	Diuretic	–3	Supramaximal cycle	↓ (18%) anaerobic capacity
	6 men	Sauna	–3	Supramaximal cycle	↓ (35%) anaerobic capacity
	5 men	Exercise	–3	Supramaximal cycle	↓ (44%) anaerobic capacity
Webster et al., 1990	7 men	Exercise in rubberized sweat suit	–5	Wingate Anaerobic Test	↓ (21%) anaerobic power ↓ (10%) anaerobic capacity
Fritzsche et al., 2000	8 men	Heat, 35°C, 25% RH	–4	Inertial load, cycling	↓ (4%)

[a] RH = relative humidity.
[b] NC = no change.

advantages conferred by high aerobic fitness and heat acclimatization (Buskirk et al., 1958; Sawka et al., 1983b). Women and men who are of comparable physical fitness and heat acclimatization status appear to respond similarly to dehydration and exercise-heat stress (Sawka et al., 1983b).

The elevated core temperature responses to dehydration result from a decrease in heat loss (Sawka and Coyle, 1999). The relative contributions of evaporative and dry heat loss during exercise depend upon the specific environmental conditions, but both avenues of heat loss are adversely affected by dehydration. Local sweating (Fortney et al., 1981, Montain et al., 1995) and skin blood flow (Fortney et al., 1984; Kenney et al., 1990) responses are both reduced for a given core temperature when a person is dehydrated. Whole-body sweating is usually either reduced or unchanged during exercise at a given metabolic rate in the heat (Sawka and Coyle, 1999). However, even when dehydration is associated with no change in whole-body sweating rate, core temperature is usually elevated; therefore, the whole-body sweating rate for a given core temperature is lower when a person is dehydrated (Sawka et al., 1984b).

Both the singular and combined effects of plasma hyperosmolality and hypovolemia have been demonstrated as mediating the reduced heat loss response during exercise-heat stress (Sawka, 1992).

Dehydration reduces a person's ability to tolerate exercise-heat stress. In experiments in the desert during 1942 and 1943, male soldiers serving as subjects attempted endurance (2 to 23 h) walks and were either allowed to drink water *ad libitum* or had to refrain from drinking (Brown, 1947c). One out of 59 (2 percent) subjects suffered exhaustion from heat strain during a desert walk when they were allowed to drink, whereas 11 of 70 (16 percent) subjects suffered exhaustion when they did not drink. In another study, "hyperacclimatized" subjects attempted a 140-minute walk in a hot environment while ingesting different combinations of salt and water (Ladell, 1955). Exhaustion from heat strain occurred in 9 of 12 (75 percent) subjects when receiving neither water or salt, and 3 of 41 (7 percent) subjects when receiving only water. More recently, normal subjects acclimated to heat attempted 140-minute treadmill walks in a hot-dry environment when euhydrated and when dehydrated by 3, 5, and 7 percent of body weight (Sawka et al., 1985). All eight subjects completed the euhydration and 3 percent dehydration experiments, while seven subjects completed the 5 percent dehydration experiments. During the 7 percent dehydration experiments, six subjects discontinued after completing an average of 64 minutes.

To address whether dehydration alters physiologic tolerance to heat strain, subjects walked to voluntary exhaustion when either euhydrated or dehydrated (8 percent of total body water) during uncompensable heat stress (Sawka et al., 1992). Dehydration reduced tolerance time from 121 to 55 min, but more importantly, dehydration reduced the core temperature that a person could tolerate. Heat exhaustion occurred at a core temperature about 0.4°C lower when dehydrated than when euhydrated.

Hyperhydration and Heat Strain

Because water deficits impair thermoregulation (e.g., body temperature increases), a logical question is whether greater-than-normal body water (hyperhydration) could improve a person's ability to thermoregulate during exercise in the heat. Many studies have examined hyperhydration effects on thermoregulation in the heat. Some investigators report lower core temperatures during exercise after hyperhydration (Gisolfi and Copping, 1974; Grucza et al., 1987; Moroff and Bass, 1965; Nielsen, 1974; Nielsen et al., 1971), while

TABLE 4-13 Dehydration Effects on Muscular Strength and Endurance

Reference	Subjects	Dehydration Process
Tuttle, 1943	13	Exercise and heat
Ahlman and Karvonen, 1961	32 men	Sauna or exercise
Saltin, 1964	10 men	Heat and exercise
Greenleaf et al., 1966	9 men	Fluid restriction
Bosco et al., 1968	9 men	Fluid restriction
Singer and Weiss, 1968	10	Fluid restriction
Bosco et al., 1974	21 men	Fluid restriction
Torranin et al., 1979	20 men	Sauna
Bijlani and Sharma, 1980	14 men	Hot room
Houston et al., 1981	4 men	Fluid restriction
Mnatzakanian and Vaccaro, 1982	Not reported	Not reported
Serfass et al., 1984	11	Fluid restriction
Webster et al., 1990	7 men	Exercise in rubberized sweat suit
Greiwe et al., 1998	7 men	Sauna
Montain et al., 1998b	5 men 5 women	Exercise and hot room

[a] NC = no change.

other studies do not (Blyth and Burt, 1961; Candas et al., 1988; Greenleaf and Castle, 1971; Latzka et al., 1997, 1998; Montner et al., 1996; Nadel et al., 1980). Some investigators report higher sweating rates with hyperhydration (Lyons et al., 1990; Moroff and Bass, 1965), while other studies do not (Blyth and Burt, 1961; Candas et al., 1988; Greenleaf and Castle, 1971; Latzka et al., 1997, 1998; Montner et al., 1996).

However, most of these studies have serious design problems, such as control conditions representing dehydration but not euhydration (Candas et al., 1988; Moroff and Bass, 1965), control conditions not adequately described (Grucza et al., 1987; Nielsen, 1974; Nielsen et al., 1971), and cool fluid ingestion that might have caused reduced core temperature (Gisolfi and Copping, 1974; Moroff and Bass, 1965). No studies were found that examined the influence of gender on thermoregulatory responses to hyperhydration. Generally, the

Δ Wt	Strength Method	Result[a]
–5%	Isometric	NC in strength
–2 kg	Isokinetic	NC in strength
–4%	Isometric	NC in strength
–7%	Isometic	NC in strength with up to 4% dehydration
–3%	Isometric	↓ (11%) in strength
–7%	Isometric	NC in strength
–6%	Isometric	↓ (10%) in strength ↓ (9%) in endurance
–4%	Isometric Isotonic	↓ (31%) in endurance ↓ (29%) in endurance
–3%	Isometric	↓ in endurance
–8%	Isokinetic	↓ (11%) in strength
–4%	Isokinetic	NC in strength NC in endurance
–5%	Isometric	NC in strength NC in endurance
–5%	Isokinetic	NC in leg strength ↓ (5%) in shoulder strength ↓ (4%) in chest strength
–4%	Isometric	NC in strength NC in endurance
–4%	Isometric	NC in strength

"best" designed studies did not report any thermoregulatory benefits from hyperhydration relative to euhydration (Greenleaf and Castle, 1971; Latzka et al., 1997, 1998; Nadel et al., 1980).

Hyperhydration and Performance

Several studies have examined whether hyperhydration improves exercise performance or heat tolerance. Blyth and Burt (1961) were the first to report the effects of hyperhydration on performance during exercise-heat stress. Their subjects ran to exhaustion in a hot climate when normally hydrated, as well as when hyperhydrated by drinking 2 L of fluid 30 minutes prior to exercise. When hyperhydrated, 13 of 18 subjects ran longer to exhaustion compared with their time to exhaustion when normally hydrated. The average time to exhaustion when hyperhydrated versus normally

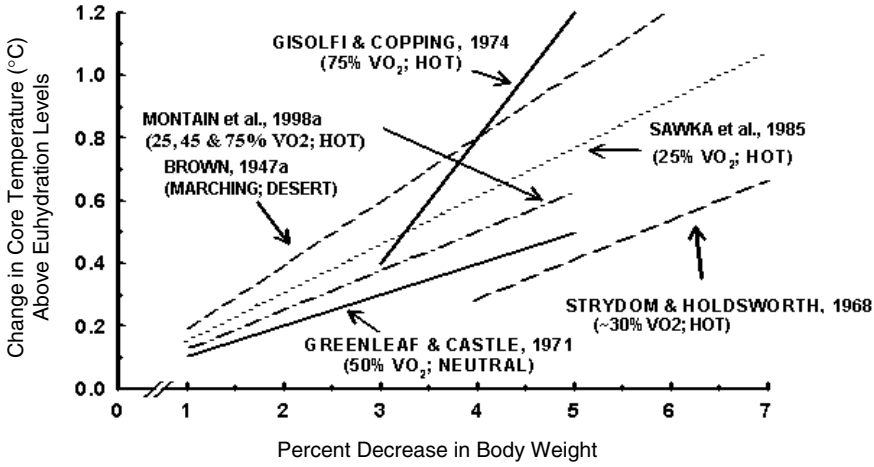

FIGURE 4-14 Relationship for elevation of core temperature (above that present with euhydration) at a given magnitude of water deficit during exercise conditions in different environments. VO_2 is maximal oxygen uptake. Adapted with permission from Sawka (1992). Copyright 1992 by Lippincott, Williams and Wilkins.

hydrated (17.3 versus 16.9 minutes) did not, however, reach statistical significance. In another study, subjects exercised to exhaustion during uncompensable exercise-heat stress when initially euhydrated (control) or hyperhydrated (increased total body water by approximately 1.5 L) (Latzka et al., 1998). Water hyperhydration did not extend endurance time beyond that seen in the control (euhydrated) condition in this study.

Dehydration and Cardiovascular Function

Dehydration increases resting heart rate when standing or lying down in temperate conditions (Rothstein and Towbin, 1947). In addition, dehydration makes it more difficult to maintain blood pressure during exposure to various perturbations. Dehydration induces fainting in individuals susceptible to postural fainting when tilted with feet down (Harrison et al., 1986; Rothstein and Towbin, 1947). Figure 4-15 presents data on a subject who was tilted with feet held downward for 10 min or until becoming unconscious (Rothstein and Towbin, 1947). With increased levels of dehydra-

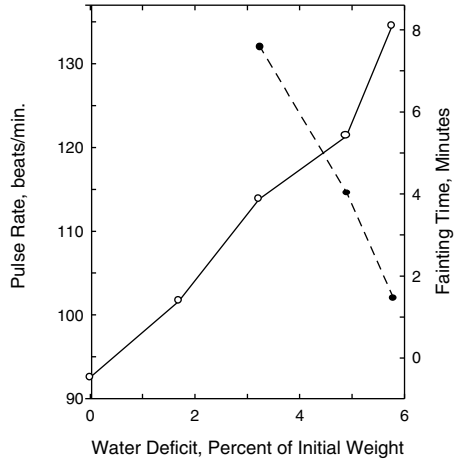

FIGURE 4-15 Relationship between body water deficit, heart rate (solid line), and fainting time (broken line) for a passively tilted subject.
SOURCE: Rothstein and Towbin (1947). Reprinted with permission from the Papers of Edward Adolph collection at the Edward G. Miner Library, University of Rochester Medical Center.

tion, the pulse rate increment increased and the time to faint decreased. Mild dehydration was recently shown to blunt baroreceptor control during an orthostatic tolerance test (Charkoudian et al., 2003), which may be an explanation for orthostatic intolerance (e.g., fainting upon standing) when an individual is dehydrated (≈ 1.6 percent of body weight). In addition, drinking water (0.5 L versus 0.05 L) markedly improved orthostatic tolerance in healthy men and women (Schroeder et al., 2002). The improved orthostatic tolerance could be mediated by plasma volume expansion or by the act of drinking resulting in increased sympathetic activation (Scott et al., 2001).

The effects of dehydration on cardiovascular responses to exercise have been investigated (Gonzalez-Alonso et al., 1997; Montain et al., 1998a; Nadel et al., 1980; Rothstein and Towbin, 1947; Sawka et al., 1979, 1985). Dehydration will increase heart rate in proportion to the magnitude of water deficit (Montain and Coyle, 1992; Montain et al., 1998a; Rothstein and Towbin, 1947; Sawka et al., 1985). Dehydration-mediated hypovolemia reduces central venous pressure (Morimoto, 1990) and cardiac filling (Coyle, 1998) and requires a compensatory increase in heart rate. During submaximal exercise with little heat strain, dehydration elicits an increase in heart rate

and a decrease in stroke volume, and usually no change in cardiac output relative to euhydration levels. Heat stress and dehydration, however, have additive effects on increasing cardiovascular strain. During submaximal exercise with moderate (Nadel et al., 1980) or severe (Gonzalez-Alonso et al., 1997; Sawka et al., 1979) heat strain, dehydration (3 to 4 percent body weight) led to a decrease in cardiac output (compared with performing the exercise task when euhydrated) because the increase in heart rate was not of sufficient magnitude to compensate for the decline in stroke volume. The dehydration-mediated reduction in cardiac output (below euhydration levels) during heat stress was greater during high intensity (65 percent VO_2max) than low intensity (25 percent VO_2max) exercise (Montain et al., 1998a). In addition, severe water deficits (7 percent of body weight) in the absence of heat strain also reduced cardiac output during submaximal exercise (Sproles et al., 1976).

Death

For obvious reasons, experimental data are not available on the effects of dehydration with death as an outcome in humans. As discussed earlier, fever is a common response to inflammation, infection, and trauma and may be augmented by dehydration (Morimoto et al., 1986; Watanabe et al., 2000). Furthermore, dehydration increases cardiovascular strain. It is suggested that dehydration might contribute to the death of hospitalized patients who are ill (Weinberg et al., 1994a).

Humans can lose 10 percent of body weight as water and have little increased risk of death unless the dehydration is accompanied by other severe stressors (Adolph, 1947a). Reports from persons in survival situations indicate that those who dehydrated to greater than 10 percent of their body weight required medical assistance to recover (Adolph, 1947a).

Experimental studies regarding dehydration and death in animals have been performed (Adolph, 1947a; Keith, 1924; Wierzuchowski, 1936). When investigators infused sugar solutions to dehydrate dogs (Keith, 1924; Wierzuchowski, 1936), most could tolerate 7 to 10 percent dehydration; however, beyond this point body temperature rose rapidly and often led to death.

Adolph (1947a) reported on experiments in which dogs were slowly dehydrated by water deprivation in temperate conditions and were then exposed to heat stress. When the dogs were dehydrated by 10 to 14 percent of body weight and exposed to heat, their core temperature "explosively increased," and they would only survive if

removed from the heat stress or given water to drink (Adolph, 1947a). Deaths began as core temperatures approached 41.6°C (107°F) and would always occur when core temperatures reached 42.8°C (109°F). Lethal core temperatures were similar in the dehydrated and euhydrated dogs (Adolph, 1947a). Cats showed similar responses, but with water deficits of up to 20 percent body weight loss and core temperatures of up to 43°C (110°F) before dying.

There are many reports from civilian and military communities of persons being stranded in very hot conditions (such as desert conditions in the summer) for extended durations in which those who had water survived and those without water died. Dehydration is believed to contribute to life-threatening heat stroke. In view of physiological changes (e.g., elevated body temperatures and reduced tissue perfusion from inadequate cardiac output), this presumed association is reasonable (Bouchama and Knochel, 2002). Dehydration contributed significantly to an outbreak of serious heat illness of Massachusetts State Police recruits who had limited water availability during summer training sessions. Eleven of a class of 50 had serious rhabdomyolysis and/or heat injury and were hospitalized—two underwent kidney dialysis and one required a liver transplant and later died (Commonwealth of Massachusetts, 1988). In 1987, three collegiate wrestlers died of cardiorespiratory arrest while undergoing severe and rapid weight loss combined with stressful exercise in the heat (Remick et al., 1998). Dehydration was implicated in these three deaths; however, those athletes appeared to be employing exercise-heat dehydration procedures that were similar to those used by other interscholastic and collegiate wrestlers. Since these were the first deaths since record keeping was initiated in 1982, it is probable that some other unknown factor may have contributed. Thus dehydration is a serious health risk, particularly when associated with febrile illness or extreme heat and exercise.

Urinary Tract Infections

Dehydration may increase the risk of infections. Hydration monitoring was assessed to determine if it would encourage individuals to increase fluid intake and thus decrease their risk for urinary tract infections (Eckford et al., 1995). Twenty-eight premenopausal women who had at least two idiopathic urinary tract infections within 6 months of the study were taught to use a simple hand-held probe (a conductivity meter) to assess their urine osmolality (Eckford et al., 1995). Although this 4-month study was only completed by 17 of the 28 women, these women increased hydration

and significantly decreased their incidence of urinary tract infection due to their greater consumption of fluids. In another study of over 300 subjects, increased fluid intake resulted in a lower rate of urinary tract infections (Pitt, 1989). While it cannot be assumed that urinary tract infections are the result of dehydration, adequate hydration may contribute to the prevention of such infections in humans (Hooton, 1995).

However, the utility of using the prevention of urinary tract infections as an indicator of adequacy is not adequately established on a quantitative basis to be used as the criterion on which to base recommended intakes of total water.

Dehydration and Chronic Diseases

Kidney Stones

Increased fluid intake has been found to be inversely associated with an increased risk of developing kidney stones (Curhan et al., 1997, 1998), and increased fluid consumption has long been suggested as means to prevent recurrence of kidney stones (nephrolithiasis). As a result of increased urine flow, the urinary concentrations of calcium, oxalate, phosphorus, and uric acid fall, thereby reducing the degree of saturation of their salts, which leads to the formation of kidney stones. Most of the available studies have been conducted on individuals who have already had stones, with the goal of preventing recurrence.

One of the first studies to evaluate the therapeutic effects of increased fluid intake was a retrospective case-series study (Hosking et al., 1983). One-hundred eight patients (83 men and 25 women) who had idiopathic calcium nephrolithiasis had been advised to increase their fluid intake to achieve a 24-hour urinary output greater than or equal to 2.5 L. Over an average follow-up period of 5 years, 58 percent of these patients had no evidence of stone growth or new stone formation (Hosking et al., 1983). In another case-series, 98 individuals (87 men, 11 women), all of whom were diagnosed as having been chronically dehydrated due to either defined history of exposure to heat due to climate or occupation or due to poor fluid intake, were asked to increase fluid intake to about 2.5 L/day (Embon et al., 1990). Resulting mean urinary volume increased from 1.7 to 2.5 L/day based on periodic random sampling during the follow-up period. After more than 4 years, the stone recurrence rate was approximately 7 percent (7/98), which

was comparatively low (Embon et al., 1990). One randomized controlled trial with 5 years of follow-up tested the effects of increased water intake as a means of preventing recurrent kidney stones in 199 individuals (134 men and 65 women) with idiopathic calcium nephrolithiasis (Borghi et al., 1996). At baseline, estimated 24-hour urine volume was approximately 1 L. During the fifth year of follow-up, 24-hour urine volume remained unchanged in the control group but increased to 2.6 L in the active treatment group. Over the course of follow-up, recurrent stones occurred in 27 percent of control participants, but in just 12 percent of those in the active treatment group ($p = 0.008$) (Borghi et al., 1996).

More recent evidence suggests that increased fluid intake may prevent the initial occurrence of kidney stones; however, data are limited. Two prospective observational studies have assessed the relationship of fluid intake with incident kidney stones, while another study assessed the relationship of specific beverages. In a study of 45,619 male health professionals without kidney stones, the adjusted relative risk of developing a stone during 4 years of follow-up was 0.71 (95 percent confidence interval [CI]: 0.52 to 0.97) comparing the highest and lowest quintiles of fluid intake (> 2.5 versus < 1.3 L/day) (Curhan et al., 1993). Similar findings were evident in a subsequent study of 91,731 female nurses without kidney stones; the adjusted relative risk of developing a stone during 12 years of follow-up was 0.61 (95 percent CI: 0.48 to 0.78) comparing the highest quintile of fluid intake (median intake of 4.7 L/day) to the lowest quintile of fluid intake (median intake of 1.9 L/day) (Curhan et al., 1997). Because the principal objective of both studies was to assess the relationship of dietary calcium intake with kidney stones, there were few analyses on the effects of fluid consumption. Subsequent reports on the beverages consumed (Curhan et al., 1996, 1998) provide data on intake of specific beverages, as well as intake of foods. A third prospective study (Hirvonen et al., 1999), which did not collect data on drinking water and total fluid intake, did report an inverse association of beer consumption with incident kidney stones.

Overall, available evidence, including the results of one clinical trial, strongly suggests that increased *total* water consumption can be effective therapy to prevent recurrent kidney stones. There is also some evidence from observational studies that increased fluid intake lowers the risk of incident kidney stones. However, this limited evidence is insufficient to set requirements for water intake as a means to prevent kidney stones.

Gallstones

Water ingestion has been shown to induce gallbladder emptying (Yamamura et al., 1988) via vagal stimulation (Svenberg et al., 1985). An association of gallstone formation (cholelithiasis) with low fluid consumption was suggested in a small group of patients (n = 30) with gallstones whose typical daily drinking water intake was estimated to be 0.4 to 0.7 L/day (Math et al., 1986). Subsequently, six individuals, one of whom had gallstones, were evaluated for the effect of water consumption on gallbladder emptying time. They consumed 0.5 L of water rapidly following an overnight fast; this resulted in gallbladder emptying within 10 to 20 minutes for those without gallstones, and 30 minutes for the patient with gallstones. It was concluded that a high daily water intake and consumption of water at regular intervals could assist with promotion of gallbladder emptying, and perhaps prevent gallstone formation (Math et al., 1986). While not tested, other beverages may have a similar effect.

Bladder, Colon, and Other Cancers

The relationship between colon cancer and total water intake has been evaluated, primarily in case-control studies. An early study that reported an inverse relationship between water consumption and colon cancer risk compared 238 men and 186 women with colon cancer to 224 men and 190 women who served as controls (Shannon et al., 1996). In the men studied, consumption of more than four glasses of water/day (~ 0.9 L) in addition to food versus one or fewer glasses/day was marginally associated with decreased colon cancer risk (odds ratio [OR] = 0.68; p = 0.16). In women, more than five glasses of water/day (~ 1.2 L) were associated with decreased colon cancer risk (OR = 0.55; p = 0.004). In another study, a fluid intake of greater than approximately 1.7 L/day was significantly associated with a decreased risk of colorectal adenoma (OR = 0.4; $p < 0.01$) (Lubin et al., 1997). Water intake levels of greater than six cups (1.4 L)/day have been reported to be protective for distal colon tumors (OR = 0.68) (Slattery et al., 1999).

Bladder cancer risk may also be reduced with increased fluid consumption. Although decreased bladder cancer risk with increased fluid intake has been reported, available studies did not all focus solely on fluid intake and bladder cancer risk (Bitterman et al., 1991; Braver et al., 1987; Pohlabeln et al., 1999; Wilkens et al., 1996). The strongest study to show a clear relationship between fluid intake and bladder cancer risk assessed the total daily fluid intake of 47,909

men (Michaud et al., 1999). Individuals who consumed greater than approximately 2.5 L/day of fluid were reported to have a 49 percent lower risk of bladder cancer than individuals who consumed less than approximately 1.3 L/day. It was also noted that the risk of bladder cancer was reduced by 7 percent for every addition of 240 mL (~1 cup) in daily fluid intake. However, several other studies have failed to demonstrate an overall association between fluid intake and bladder cancer risk (Bruemmer et al., 1997; Geoffroy-Perez and Cordier, 2001; Slattery et al., 1988).

Arrhythmias

One study has reported electrocardiogram (ECG) changes associated with varying levels of water deficit (Sawka et al., 1985). ECG abnormalities (arrhythmias and premature ventricular contractions) during exercise in the heat in healthy young adults who were dehydrated at 5 percent or greater of body weight loss were assessed (Sawka et al., 1985). All eight subjects completed 140 min of exercise without any ECG abnormalities when euhydrated or when dehydrated by 3 percent of body weight. Numerous premature ventricular contractions during exercise-heat trials at 5 and 7 percent dehydration were seen on the remaining subjects.

In another report, three collegiate wrestlers died of cardiorespiratory arrest while undergoing severe and rapid weight loss combined with stressful exercise in the heat (Remick et al., 1998). Because neither cardiorespiratory arrest nor heat injury/stroke had been previously reported with the rapid and severe dehydration procedures used in scholastic or collegiate wrestling, and because these deaths occurred over a short period of time, perhaps an unknown factor may have contributed. However, it is possible that the fluid-electrolyte imbalances resulting from marked dehydration, particularly if combined with stressful exercise, may contribute to ECG abnormalities in some individuals.

Ingestion of cold fluids has been thought to induce cardiac arrhythmias. However, the research in this area is equivocal. Electrocardiogram (ECG) changes after consumption of ice-cold beverages in healthy individuals without known cardiac or gastrointestinal problems were assessed (Pratte et al., 1973). In this controlled study, after ingestion of cold water there were significant changes in the ST segment. These segment changes were greater with larger volumes of cold water ingestion. Conversely, significant ECG changes (using a Holter monitor) were not seen in individuals who consumed iced fluids in another study (Haughey, 1990). Hence,

available data on the effects of cold fluid ingestion as a risk factor for arrhythmia are sparse and inconsistent.

Blood Clots

Few studies have been conducted on the effects of fluid intake on factors that may increase blood clots. In one study, water and an electrolyte-carbohydrate beverage were compared to assess which would maintain hydration and decrease blood viscosity during a 9-hour plane flight (Hamada et al., 2002). Forty healthy men (mean age 23 years) were given approximately 1.3 L of either an electrolyte-carbohydrate beverage or water in five servings during the long flight. Compared with the water group, the men given the electrolyte-carbohydrate beverage gained more body weight, had lower urine output, and had improved net fluid balance. In addition, those who consumed the electrolyte-carbohydrate beverage had less viscous blood than those who drank water. Based on this one study, it appears that on long flights the concomitant consumption of fluid and solute may be more suitable to maintain hydration status and decrease blood viscosity than water alone; however, additional studies are needed to validate this effect.

Mitral Valve Prolapse

The effects of dehydration on mitral valve prolapse (MVP) have been evaluated in order to assess if dehydration could be used as a diagnostic tool for MVP (Lax et al., 1992). MVP, or symptoms associated with it, was induced by mild dehydration and, upon rehydration, the symptoms disappeared (Aufderheide et al., 1994; Lax et al., 1992). A lower atrial filling pressure and volume would result in a floppy valve balloon (prolapse more). It has been recommended that hydration status should be considered if a person with MVP is suspected of having atypical chest pain or palpitations (Aufderheide et al., 1994; Lax et al., 1992).

Osteoporosis

Longitudinal research on the effects of fluid intake on bone mineral density and osteoporosis has not been conducted. However, some short-term studies evaluating bone mineral density changes due to hydration status or the type of ingested fluids are available. The extent to which drinking various amounts of fluids between meals, and the meals themselves, affected body composition and

bone mineral density were assessed in healthy individuals or individuals undergoing hemodialysis (Horber et al., 1992). No changes in bone mineral density as a result of the meals or hydration status were detected.

In a subsequent study, the calcium content of the water or beverage may have a greater impact on bone mineral density than the amount of fluids in terms of volume consumed (Costi et al., 1999).

FACTORS AFFECTING WATER REQUIREMENTS

Environmental Factors

Physical Activity and Heat Strain

Physical activity and heat strain can elicit high rates of total water loss via sweat loss. A person's sweating rate depends on the climatic conditions, clothing worn, and exercise intensity and duration. In temperate conditions, the capacity for dry heat loss reduces evaporative heat loss requirements, so sweat losses are relatively low. It is not unusual for female and male distance runners to have sweating rates of approximately 0.7 and 1.0 L/hour, respectively, in temperate conditions (Cheuvront and Haymes, 2001). The level of physical fitness has a modest effect on sweat losses, unless accompanied by heat acclimatization. For persons to sustain high-intensity exercise in the heat or perform strenuous labor activities for an entire day in the heat, they would need to be well heat acclimatized.

Exposure to climatic heat stress will increase fluid[3] requirements for a given physical activity level. Persons in very hot (e.g., desert) climates often have sweating rates of 0.3 to 1.2 L/hour while performing occupational activities (Gosselin, 1947). Persons wearing protective clothing often have sweating rates of 1 to 2 L/hour while performing light-intensity exercise in hot weather (Levine et al., 1990; Montain et al., 1994). Male competitive runners can have sweating rates of 1.0 to greater than 2.0 L/hour while training or racing in the heat (Armstrong et al., 1986; Costill, 1977; Costill et al., 1970). Female competitive runners may increase their sweat losses

[3] The word "fluid" is used because that is the component of *total* water consumption that varies markedly on a daily basis due to thirst and other factors. It is assumed, unless otherwise noted, that a more constant component of the daily *total* water intake is derived from food (as metabolic and compositional water provided by food and beverages).

from approximately 0.7 L/hour in temperate weather to approximately 1.1 L/hour in warm weather when performing the same event (Cheuvront et al., 2002). Clearly these exertional rates cannot be sustained for 24 hours. The effect of sustaining these high sweating rates can markedly increase daily total water requirements. For example, the daily fluid intake of soldiers performing either "normal" work (~ 3,350 kcal/day) or physical training (~ 5,500 kcal/day) over a 12-day period in hot climate (mean daytime conditions 40°C [104°F] and 29 percent relative humidity) averaged approximately 7 and 11 L/day for the "normal" and physical training groups, respectively (Mudambo et al., 1997b).

Several analyses have attempted to quantify the effects of hot weather on increasing daily fluid (total water) requirements (Brown, 1947b; Lee, 1964; Sawka and Montain, 2001; U.S. Army, 1959). These analyses (Figures 4-16, 4-17, and 4-18) suggest that daily fluid

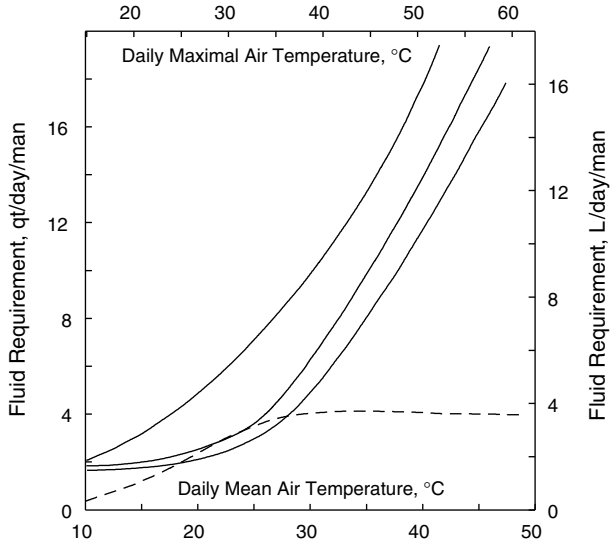

FIGURE 4-16 Daily fluid (water) requirements in soldiers as related to air temperature and activity from studies conducted by Brown (1947b). Top line represents "hard work" 8 h/day. Second line represents the same work but performed at night. Third line represents resting in shade. Bottom line represents the amount of water saved by working at night. Reprinted with permission from the Papers of Edward Adolph collection at the Edward G. Miner Library, University of Rochester Medical Center.

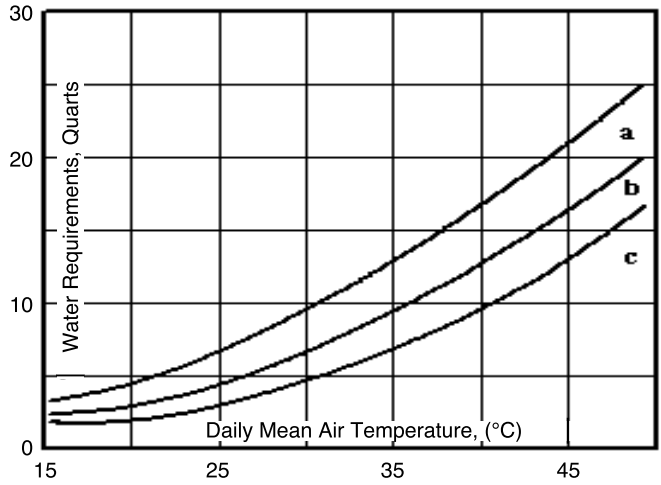

FIGURE 4-17 Daily fluid (water) requirements as related to air temperature and activity from studies conducted by the U.S. Army and used previously to estimate water requirements (1959). Top line (a) represents "hard work" in sun for 8 h/day. Second line (b) represents moderate work in sun for 8 h/day. The bottom line (c) represents resting in shade for 8 h/day.

requirements range in sedentary, active, and very active persons from 3 to 6 L/day in temperate climates and from 4 to 12 L/day in hot climates (Brown, 1947b; Lee, 1964; Sawka and Montain, 2001; U.S. Army, 1959).

Fluid requirement data, based on intake, was reported in 1947 for soldiers working in different climates (Brown, 1947b). Figure 4-16 provides their reported relationships between daily maximal and mean air temperature values at two levels of physical activity on daily fluid requirements (qt/day, 1 qt = 0.95 L). This analysis did not specify the exact metabolic rates (kcal/day) or climatic heat stress encountered (e.g., radiant heat, humidity, air motion), and the experiments were mostly conducted in desert climates. Note that if the daily mean temperature was 30°C (86°F), the daily fluid requirements approximated ≈ 10 qt (9.5 L) if working 8 hours per day or ≈ 5 qt (4.5 L) if resting in the shade. Figure 4-16 suggests that in extreme heat stress and activity conditions, the daily fluid requirements could be greater than 16 qt (15.2 L). However, most persons reduce their activity level in hot weather, so such high daily fluid requirements would be for very physically fit, heat acclima-

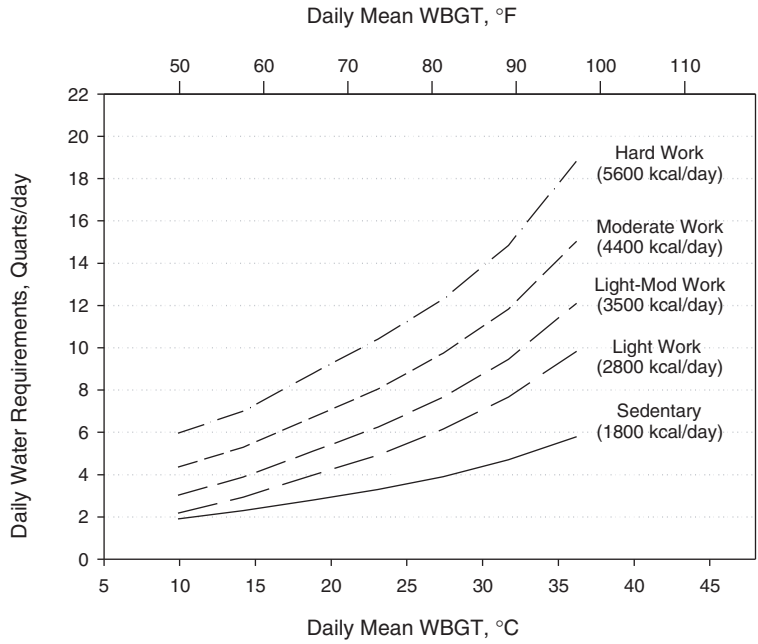

FIGURE 4-18 Approximate daily water requirements as a function of climatic temperature (Wet Bulb Globe Temperature, WBGT) and total energy expenditure (kcal). Reprinted with permission from Sawka and Montain (2001). Copyright 2001 by International Life Sciences Institute.

tized persons forced to work at very high metabolic rates for an extended period of time.

Figure 4-17 presents a graph published a number of years ago by the U.S. Army (1959) that displays daily fluid (water) requirements for soldiers living in hot climates under three conditions. It should be noted that no indication was given as to the type of data used to develop this graph. The analysis did not specify the exact metabolic rates (kcal/day) or climatic heat stress (e.g., radiant heat, humidity, air motion). Note that if the daily mean temperature was 30°C (86°F), the daily water requirements estimated in this graph approximate 12 qt (11.4 L) if working 8 hours per day and 4 qt (3.8 L) if resting in the shade. The figure suggests that in extreme heat stress and activity conditions, the daily water requirements could be greater than 20 qt (19 L).

Daily fluid (water) requirements have been estimated based upon mathematical modeling of sweating rates for a given environmental

condition (Sawka and Montain, 2001). The sweating rates were predicted by using an equation that includes the effects of metabolic rate, climate, and clothing (Moran et al., 1995; Shapiro et al., 1982, 1995). Physical exercise and rest were varied (a 12-hour work period was used) to achieve a variety of total energy expenditure rates at different climatic conditions. Climatic heat stress was quantified by mean daily Wet Bulb Globe Temperature (WBGT), which combines the effects of ambient temperature, humidity, solar load, and wind (Sawka et al., 1996a). Figure 4-18 presents the range of daily fluid (water) requirements of persons performing light (1,800 total kcal/day) through hard (5,640 total kcal/day) work in climates with mean daytime WBGT ranging from 5° to 35°C (41° to 95°F). Note that daily fluid requirements increase with metabolic rate and heat stress. For sedentary to very active persons, daily fluid requirements range from 2 to 4 qt/day (1.9 to 3.8 L/day) in a cool climate and up to 8 to 16 qt/day (7.6 to 15.2 L/day) in very hot climates. For example, in Atlanta, Georgia, the mean daily WBGT temperature is approximately 30°C (86°F) during mid-summer, and persons living there will have daily fluid requirements of 4 to 14 qt/day (3.8 to 13.3 L/day), depending upon their activity levels and duration of exposure (e.g., sitting in air conditioning is not heat exposure). Generally, physical activity is curtailed in hot weather, so high levels of water intake, such as 14 qt/day (13.3 L/day), are rare.

The maximal hourly fluid replacement rate approximates the sweating rates often observed during intense physical exercise in the heat. This upper limit for fluid replacement rate during exercise-heat stress is determined by the gastric emptying rate, as maximal intestinal absorption is not limiting (Gisolfi and Ryan, 1996). The maximal gastric emptying rate approximates 1.0 to 1.5 L/hour for an average adult man (Mitchell and Voss, 1991; Murray, 1987) but has considerable individual variability and is influenced by gastric volume (the higher the volume, the greater the emptying rate). Gastric emptying rates are reduced somewhat during high- (greater than 75 percent VO_2max) intensity exercise (Costill and Saltin, 1974; Neufer et al., 1989b), dehydration (Neufer et al., 1989a; Rehrer et al., 1990), and heat strain (Neufer et al., 1989a; Rehrer et al., 1990). Dehydration probably mediates reduced gastric emptying by increasing heat strain, as an inverse relationship ($r = -0.76$) between the fluid volume emptied and core temperature has been observed (Neufer et al., 1989a).

This is consistent with observations by Rehrer and colleagues (1990), who found that dehydration reduced gastric emptying rate during exercise when core temperature was elevated above

euhydration levels, but not at rest when core temperature was not elevated. Likewise, Ryan and colleagues (1998) found that dehydration (approximately 3 percent of body weight) did not influence gastric emptying or intestinal absorption during exercise without marked heat strain. Their subjects had final exercise core temperatures of 38.5°C (101.3°F), which was approximately the core temperature where the subjects of Neufer and colleagues (1989a) began to clearly demonstrate reduced gastric emptying.

Altitude and Cold

Altitude exposure will result in dehydration because of elevated respiratory water losses (approximately 200 mL/day above the usual baseline of 250 mL/day), hypoxia-induced diuresis, reduced fluid consumption (approximately 2 to 3 L over several days), and possibly elevated sweating from the high metabolic rates needed to traverse rugged mountain terrains (Anand and Chandrashekhar, 1996; Hoyt and Honig, 1996). The net effect is a total body water deficit reduction during altitude exposure (Anand and Chandrashekhar, 1996; Hoyt and Honig, 1996). In lowlanders exposed to moderate altitude (> 2,500 m), hypoxia will rapidly initiate diuresis that continues for several days (Anand and Chandrashekhar, 1996; Hoyt and Honig, 1996). This diuresis and the factors discussed above decrease total body water and plasma volume in proportion to the elevation of ascent (Sawka et al., 2000). Mechanisms responsible for the resultant hemoconcentration include diuresis, natriuresis, and dehydration, as well as loss of circulating plasma protein (Anand and Chandrashekhar, 1996; Hoyt and Honig, 1996; Sawka et al., 2000). This hemoconcentration is isoosmotic (unless sweat-induced dehydration contributes) and exceeds the reduction in total body water because it is largely oncotically mediated (Sawka et al., 1996b).

Body water reduction and hemoconcentration are believed to provide several physiological benefits by contributing to the increased oxygen content (Sawka et al., 2000) and perhaps reduced risk of mountain sickness (e.g., Acute Mountain Sickness, pulmonary edema, cerebral edema) (Anand and Chandrashekhar, 1996). The effects of dehydration on mountain sickness and performance decrements at altitude have not been studied.

Body fluid losses in cold climates can be as high as losses in hot climates due to high rates of energy expenditure and use of heavy clothing (Freund and Young, 1996). Fluid losses during cold exposure are commonly thought to result from cold-induced diuresis

and increased respiratory water losses (see Table 4-3). Cold-induced diuresis (CID) is well studied and is a "normal" physiological response to body cooling. Urine specific gravities decrease with CID; however, they cluster around 1.009 (Bass and Henschel, 1956). CID induces an isoosmotic hemoconcentration, and there is little relationship between the magnitude of diuresis and hemoconcentration (Bass and Henschel, 1956; Young et al., 1987). The reduction in body water with contracting vascular volume is probably of no concern as long as the body remains cool.

Dehydration does not modify thermoregulation during cold exposure as evidenced by body heat balance (O'Brien et al., 1998) or peripheral vascular responses (O'Brien and Montain, 2003). However, if the dehydrated person were to subsequently exercise and produce body heat while wearing highly insulating clothing, then heat stress will be encountered. (The effects of dehydration and heat stress on thermoregulation and physical work performance have been discussed earlier in this chapter.)

Dietary Factors

Caffeine

Caffeine is one of three methylxanthines found in foods; it is naturally present in coffee, teas, and chocolate, is added to colas and other beverages (IOM, 2001a), and is a component of many medications (Passmore et al., 1987). It is estimated that 20 to 30 percent of Americans consume more than 600 mg of caffeine daily (Neuhauser-Berthold et al., 1997). The other two methylxanthines, theobromine (found in chocolate) and theophylline (found in tea), demonstrate some, but not all, of the pharmacological effects of caffeine (Dorfman and Jarvick, 1970).

It has long been thought that consumption of caffeinated beverages, because of the diuretic effect of caffeine on reabsorption of water in the kidney, can lead to a total body water deficit. However, available data are inconsistent. As early as 1928 it was reported that caffeine-containing beverages did not significantly increase 24-hour urinary output (Eddy and Downs, 1928). Caffeine-containing beverages did not increase 24-hour urine volume in healthy, free-living men when compared with other types of beverages (e.g., water, energy-containing beverages, or theobromine-containing beverages) (Dorfman and Jarvik, 1970; Grandjean et al., 2000).

Conversely, in a study in which 12 individuals who normally consumed caffeinated beverages were required to abstain from all

methylxanthine-containing foods and drugs for 5 days and who were then were given 642 mg of caffeine in the form of coffee, 24-hour urine output increased by 0.75 ± 0.53 L, a 41 percent increase (Neuhauser-Berthold et al., 1997). Given that the study design did not evaluate habitual intake, it is difficult to determine the extent to which this large amount of caffeine would impact total water needs on a chronic basis.

In an earlier study, the effect of caffeine intake on urinary output was evaluated in eight men who were asked to consume four cups of coffee or six cups of tea/day (providing approximately 240 mg of caffeine/day) for 5 days prior to data collection and then to abstain from caffeine 24 hours prior to data collection (Passmore et al., 1987). The subjects were then given various doses of caffeine (45, 90, 180, or 360 mg) on the study day. Cumulative urine volume 3 hours after consuming the test dose was increased significantly only at the 360-mg dose of caffeine. This is equivalent to four cups of regular brewed coffee (USDA/ARS, 2002).

Caffeine can induce hemodynamic effects not directly related to fluid balance. The acute pressor effects (e.g., vasoconstriction, palpitations) of caffeine consumption are well documented; however, in a review of the relevant literature, there was no clear epidemiologic evidence that habitual caffeine consumption leads to hypertension (Nurminen et al., 1999).

In aggregate, available data suggest that higher doses of caffeine (above 180 mg/day) have been shown to increase urinary output, perhaps transiently, and that this diuretic effect occurs within a short time period (Passmore et al., 1987). Whether or not caffeine ingestion at high amounts leads to a total body water deficit is uncertain (IOM, 2001a), although some have tried to develop a predictive model of water needs based on the limited data available (Stookey, 1999). Hence, unless additional evidence becomes available indicating cumulative total water deficits in individuals with habitual intakes of significant amounts of caffeine, caffeinated beverages appear to contribute to the daily *total* water intake similar to that contributed by noncaffeinated beverages.

Alcohol

Similar to caffeine, the diuretic effect of alcohol is mediated by the suppression of arginine vasopressin (Stookey, 1999). Increased diuresis was reported during the initial 3 hours of consuming a beverage in which alcohol (ethanol) was present (consumed at level of 1.2 g/kg of body weight in a solution of fruit juice) in healthy,

adult men (Taivainen et al., 1995). Nonetheless, 6 hours after ingestion, there was an antidiuretic phase, which lasted up to 12 hours post-alcohol ingestion (Taivainen et al., 1995). This could have been a result of a high serum osmolality that stimulated arginine vasopressin, resulting in water reabsorption (Taivainen et al., 1995). The effects of ethanol appear to change during the course of the day and may depend on the amount of water consumed at prior meals (Stookey, 1999). Thus, based on these limited data, it appears that the effect of ethanol ingestion on increasing excretion of water appears to be transient and would not result in appreciable fluid losses over a 24-hour period.

Macronutrients

Urea, a major end product of metabolism of dietary proteins and amino acids, requires water for excretion by the kidneys. Renal excretion of 1 g of urea nitrogen (2.2 g of urea) requires 40 to 60 mL of water. Thus, if a person consumes 63 g of protein in a diet that contains 2,100 kcal, the volume of water required increases by 0.4 to 0.6 L/day above the basal osmolar excretory requirement of 0.5 and 0.75 L/day in younger and older individuals, respectively. Increasing dietary protein did not affect water intake or urine volume in eight men fed constant diets with 80 versus 180 g/day of protein for 7 days while energy and sodium intake remained constant (Luft et al., 1983). *Ad libitum* water intake was reported to be 2.8 and 2.7 L/day and urine volume was 2.1 and 2.0 L/day, respectively. Although changes in solute and urea nitrogen excretion were reported, these changes were appropriate for the changes in protein intake. Thus increased protein intake did not affect water intake or urine volume in the setting of *ad libitum* water consumption.

Like protein, the presence of dietary carbohydrate may also affect water requirements. On average, 100 g/day of carbohydrate is needed to prevent ketosis (IOM, 2002/2005). This amount of carbohydrate has been shown to decrease the body water deficit by decreasing the quantity of body solutes (ketone bodies) that need to be excreted (Gamble, 1947). This response is similar when ketosis occurs with consumption of very low carbohydrate diets.

Fecal water losses are increased with increased dietary fiber. The effects of adding 5.1 g/day of crude fiber to the diet of 20 nuns who ranged in age from 25 to 72 years were evaluated (Baird et al., 1977); mean total daily crude fiber intake was 8.4 g (Baird et al., 1977). After 12 weeks, consumption of a high-fiber biscuit resulted in a significant increase in fecal water loss compared with a placebo

biscuit (107 versus 67 mL/day, $p < 0.01$) (Baird et al., 1977). Other studies have also demonstrated increased stool weight due to increased fecal water during periods of increased dietary fiber intake (Cummings et al., 1976; Floch and Fuchs, 1978).

Sodium Intake

The effects of increased sodium intake on urine volume, a proxy of water intake, have been assessed in two experimental studies (He et al., 2001; Luft et al., 1983). In one study, 24 men were given 0.23, 4.6, and 9.2 g (10, 200, and 400 mmol)/day of sodium for 7 days while energy, potassium, and protein intake were maintained at a constant level (Luft et al., 1983). In spite of a 40-fold increase in sodium intake, little change was noted in urine volume (which averaged 2.1 L on the lowest sodium intake level and 2.3 L on the highest). In a second study, 104 hypertensive subjects (48 men and 56 women) were studied after 5 days on approximately 8 g (350 mmol)/day of sodium and again after 5 days on 0.23 to 0.5 g (10 to 20 mmol)/day (He et al., 2001). Twenty-four-hour urine excretion volume was 2.2 L at the higher sodium level, but significantly less, just 1.3 L, on the lower sodium level. In separate analyses of data from the Intersalt study, it was estimated that a 2.3 g (100 mmol)/day reduction in sodium intake should decrease 24-hour urine volume by 0.38 and 0.40 L in hypertensive and nonhypertensive individuals, respectively (He et al., 2001). Overall, based on these limited data, it is not possible to determine the extent to which sodium intake influences water intake.

Pathophysiologic Factors

Diabetes Mellitus

There is no evidence that increased water intake influences the detection of diabetes mellitus or alters the diagnostic approach to this illness. However, dehydration is clearly associated with worsening of diabetes control. In addition, uncontrolled diabetes mellitus dramatically enhances the development of severe dehydration and volume depletion due to osmotic diuresis. The changes in acid-base balance and increased osmolality of urine from hyperglycemia-induced glycosuria and ketoaciduria increase urine output. In poorly controlled diabetic individuals, reduced water intake can also lead to dehydration as a result of infection or hypotension, which can lead to delirium and impaired ability to seek water.

While two-thirds of diabetic ketoacidosis and hyperglycemic hyperosmolar states are associated with infections, many episodes develop with minimal or no apparent causation. In these settings, dehydration may be the clinical presentation of the altered diabetic state and can be quite profound, with deficits of whole-body water exceeding 5 L. In these individuals, weakness and confusion further reduce fluid intake and lead to greater dehydration.

Cystic Fibrosis

The concentration of sodium chloride in the sweat of patients with cystic fibrosis (CF) is considerably higher than that of age-matched healthy individuals. In some patients, sweat sodium and chloride levels may approach their plasma concentrations. In contrast, sweat sodium and chloride levels of healthy individuals seldom exceed 60 to 70 mmol/L. As a result, patients with CF may lose excessive amounts of sodium chloride, particularly when their sweating rates are elevated during physical exercise or exposure to climatic heat (Bar-Or et al., 1992; Kriemler et al., 1999; Orenstein et al., 1983).

Unlike healthy people, whose body fluid osmolality rises as a result of sweating, the osmolality of CF patients does not increase due to high concentrations of sodium and chloride in their sweat. The excessive loss of these ions results in significantly lower serum sodium and chloride concentrations, as well as lower serum osmolality. Furthermore, drinking water while exercising in the heat can also contribute to the decrease in serum osmolality experienced by CF patients (Kriemler et al., 1999; Orenstein et al., 1983). Without elevated serum osmolality, these patients are deprived of a major trigger for thirst and, as a result, dehydration ensues. A study with 10- to 14-year-old CF patients showed that during a 3-hour intermittent exercise program in 31° to 33°C (88° to 91°F), voluntary drinking of water was only half that of age-matched controls, and the CF patients' level of dehydration was threefold that of the controls (Bar-Or et al., 1992) (Figure 4-19).

One can stimulate the thirst of patients with CF, as with healthy individuals, by increasing the sodium chloride content in the fluid ingested. Indeed, when 11- to 19-year-old patients with CF were given a flavored drink containing 50 mmol/L of sodium chloride, their voluntary drinking increased, which was sufficient to prevent dehydration during a 3-hour exposure to exercise in the heat. Lower concentrations of sodium chloride in the drink were insufficient to trigger adequate drinking (Kriemler et al., 1999).

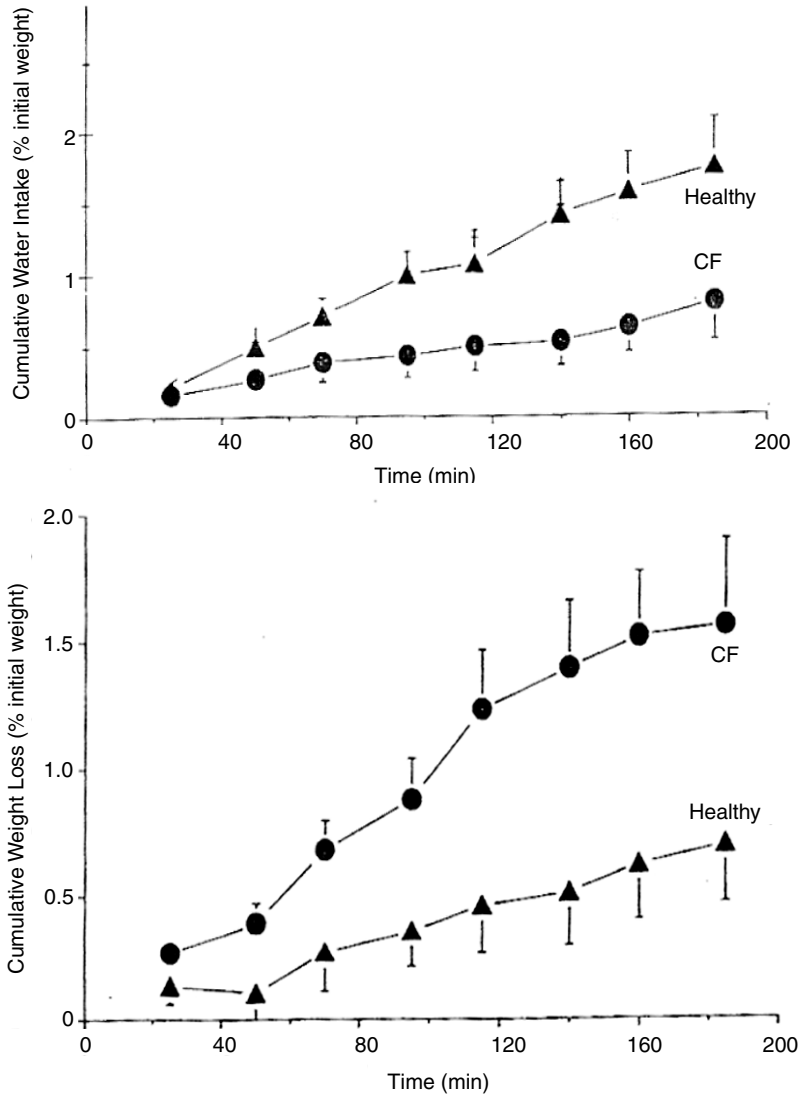

FIGURE 4-19 Cumulative voluntary water intake (top graph) and involuntary dehydration (bottom) in 10- to 14-year-old girls and boys with cystic fibrosis and in healthy controls, during intermittent exercise in hot climate. Reprinted with permission, from Bar-Or et al. (1992). Copyright 1992 by Elsevier.

Renal Disease

Studies have been conducted to assess whether increased water intake will prevent renal disease (aside from kidney stone formation, as discussed earlier). The association between consumption of varying amounts of water intake and renal function was assessed in a study of eight men and one woman (Shore et al., 1988). As expected, urine volume decreased during water restriction and urine volume increased with water loading. These changes occurred without any effects on atrial natriuretic peptide levels. Plasma arginine vasopressin and plasma and urine osmolality were increased during water restriction and decreased during the water loading period (Shore et al., 1988). Similar changes in plasma osmolality and arginine vasopressin levels have been reported during water loading (Kimura et al., 1976). While no specific data were identified that would indicate that the volume of water consumed on a chronic basis was related to subsequent development of kidney diseases, such as glomerulonephritis or end-stage renal disease, total water consumption must be adequate to allow excretion of variable amounts of osmotically active ions and compounds that are the end products of dietary intake and metabolism; in healthy-functioning kidneys, it appears that homeostatic changes typically maintain water balance in spite of the wide range of dietary intakes (Shore et al., 1988).

Diuretics and Medication Use

There are no medications that directly stimulate water intake. However, certain anticholineric drugs may do so indirectly by producing a dry mouth. Also, in settings where decreased fluid intake has occurred, medications that improve metabolic and cognitive function should indirectly assist individuals to increase fluid intake. Examples of such medications include antibiotics for infection, insulin for unstable diabetes, and analgesics to control pain that has produced delirium. Antidepressant therapy may also stimulate improved fluid intake.

On the other hand, some medications produce excess water loss. In the situation of diuretic use, unintentional dehydration may occur when individuals reduce their fluid intake for some illness or behavior-related reason, yet continue with their diuretic treatments. This may occur clinically when a heart failure patient on chronic diuretics undergoes a bowel preparation for elective colonoscopy and loses excess fluid through the gastrointestinal tract during the preparation. Dehydration may also occur if the individual does not

modify the chronic use of diuretics in situations where excess water losses occur (e.g., prolonged environmental heat).

Some medications, such as lithium, may interfere with regulatory systems for the control of arginine vasopressin release and result in a central or nephrogenic diabetes insipidus (Posner and Mokrzycki, 1996; Stone, 1999). In this setting, water losses through the kidney increase dramatically as arginine vasopressin is unavailable to stimulate water reabsorption back into the collecting tubules.

FINDINGS BY LIFE STAGE AND GENDER GROUP

Infants Ages 0 Through 12 Months

Evidence Considered in Setting the AI

As is described in Chapter 2, unless there is reason to believe that human milk is inadequate in meeting an infant's need for a nutrient, an adequate intake (AI) is derived for infants based on data regarding human milk consumption for this age group.

Water Production and Losses. Infants ages 0 to 12 months merit special consideration regarding water losses and requirements. Compared with children and adults, infants have a higher total body water content per kg of body mass (Altman, 1961), a higher surface area-to-body mass ratio, a higher rate of water turnover (Fusch et al., 1993), a less-developed sweating apparatus (Kuno, 1956), a limited ability to excrete solutes, and a lower ability to express thirst.

During the first year of life, more than half of daily water losses occur through urine (Goellner et al., 1981; NRC, 1989). Insensible loss accounts for approximately 40 percent and stool for approximately 5 percent. Most studies report daily urine losses of approximately 90 to 110 mL/kg of body weight. Based on periodic monitoring of 15 healthy, full-term infants undergoing metabolic balance studies, daily urine volume was 59 percent of volume intake in the first month of life. It gradually decreased, reaching 47 percent in months 6 to 12, and again rose to just over 50 percent during months 12 to 32 (Goellner et al., 1981).

It is not known what percentage of insensible water loss is respiratory loss versus losses from the skin. Sweating can occur soon after birth, but not in all infants. In one study, 64 percent of full-term newborns excreted sweat within several hours of birth when they were exposed to a warm environment in the nursery (Agren et al., 1997). Some evidence exists, however, that the sweating apparatus is not fully developed before the third year of life (Kuno, 1956).

Very little information is available on metabolic water production in infants. In one study, the metabolic water production in 10- to 15-month-old infants was 13 percent of water turnover (Fusch et al., 1993), a value similar to that found in adults.

Milk Consumption. Infants exclusively fed human milk do not require supplemental water. This is true not only during temperate climatic conditions, but also in hot and humid climates (Almroth and Bidinger, 1990; Cohen et al., 2000). It is also true for term infants with low birth weight (Cohen et al., 2000).

Average *total* daily intake of water of all sources in the first year of life was 130 mL/kg/day based on data from 296 infants in the 1994–1996 Continuing Survey of Food Intake by Individuals (CSFII) conducted by the U.S. Department of Agriculture (Heller et al., 2000). This *total* intake of water decreased significantly to 108 mL/kg/day in year two. Non-Hispanic blacks had the highest total water consumption (129 mL/kg/day), while non-Hispanic whites had the lowest consumption (113 mL/kg/day) (Heller et al., 2000).

As discussed in Chapter 2, the average volume of human milk consumed during the first 6 months of life is estimated to be 0.78 L/day. Because approximately 87 percent of the volume of human milk exists as water, approximately 0.68 L/day (0.78 × 0.87) of water is consumed. Therefore the AI for *total* water for infants 0 through 6 months of age is set at 0.7 L/day after rounding to the nearest 0.1 L.

Milk volume for infants 7 to 12 months of age has been estimated to be 0.6 L/day (see Chapter 2). Water intake for older infants can be determined by estimating the water intake from human milk (concentration × 0.6 L/day) and from complementary foods and other beverages (see Chapter 2). Water intake data from complementary foods and beverages other than human milk was estimated to be 0.32 L/day based on data from the CSFII (Appendix E).[4] The average water intake from human milk is approximately 0.52 L/day (0.87 × 0.6 L/day). Thus the *total* water intake is estimated to be 0.84

[4] The sample population includes breastfeeding infants with two 24-hour diet recalls; infants consuming more than 62 g (approximately ¼ cup) fluid milk and/or infant formula on either of the survey days were not included in the analyses. Means and standard errors were calculated with WesVar Complex Samples 3.0. Total water intake reflects the sum of plain drinking water and the water content of all foods and beverages consumed. Data on plain drinking water intake were provided by a proxy in response to the question, "How many fluid ounces of plain drinking water, that is, tap water or any bottled water that is not carbonated, with nothing added to it, did you drink yesterday?"

L/day (0.32 + 0.52). The AI is set at 0.8 L/day after rounding to the nearest 0.1 L. Based on CSFII, approximately 26 percent of *total* water intake is from foods, whereas 74 percent is from beverages (including formula and drinking water) for infants 7 to 12 months of age.

Total Water AI Summary, Ages 0 Through 12 Months

AI for Infants	
0–6 months	**0.7 L/day of water, assumed to be from human milk.**
7–12 months	**0.8 L/day of *total* water, assumed to be from human milk, complementary foods and beverages. This includes approximately 0.6 L (≈ 3 cups) as total fluid, including formula or human milk, juices, and drinking water.**

Children and Adolescents Ages 1 Through 18 Years

Evidence Considered in Setting the AI

In general, the differences in body water content between children, adolescents, and adults are smaller than between infants and children. This is shown in Table 4-1 for total body water as a fraction of body mass (Altman, 1961). A gradual, modest decline during childhood and adolescence in total body water per fat-free mass and per body mass in shown in Figure 4-1 (Van Loan and Bolieau, 1996).

Based on water balance studies, daily water intake increases twofold between the first month of life and months 6 to 12 (Goellner et al., 1981). In contrast, the increase in the daily intake between the ages of 2 and 9 years is only about 5 to 10 percent (Table 4-4). Likewise, based on doubly labeled water measurements, daily water turnover per body mass declines rapidly between infancy and early childhood, but thereafter, the decline is modest.

There are a number of indicators that can be used for assessing water status; however, because of homeostatic responses, some degree of over- and underhydration can be compensated for over the short term. Therefore, there is not a single water intake level that can be recommended for ensuring adequate hydration and optimal health. Data from Third National Health and Nutrition Examination Survey (NHANES III) demonstrate that normal hydration status for children (12 to 18 years of age), as measured by serum osmo-

lality, can be achieved with a wide range of *total* water intakes (e.g., first through 99th percentile of total water intake) (Appendix Table G-1). Therefore, the AI for *total* water is set based on the median *total* water intake using data from NHANES III (Appendix Table D-1) and rounding to the nearest 0.1 L.

Based on these data, the median *total* water intake for children 1 to 3 years of age was 1.3 L/day, children 4 to 8 years was 1.7 L/day, boys 9 to 13 years was 2.4 L/day, boys 14 to 18 years was 3.3 L/day, girls 9 to 13 years was 2.1 L/day, and girls 14 to 18 years was 2.3 L/day.

The percent of *total* water that was consumed from foods was 29 percent for ages 1 to 3 years (0.38 L/day), 29 percent for ages 4 to 8 years (0.51 L/day), 24 percent for boys 9 to 13 years (0.58 L/day), 20 percent for boys 14 to 18 years (0.67 L/day), 24 percent for girls 9 to 13 years (0.52 L/day), and 20 percent for girls 14 to 18 years (0.46 L/day) (derived from Appendix Table D-1 and D-4, by dividing the median in Table D-4 by the median in Table D-1).

Total Water AI Summary, Ages 1 Through 18 Years

AI for Children	
1–3 years	**1.3 L/day of *total* water. This includes approximately 0.9 L (≈ 4 cups) as total beverages, including drinking water.[5]**
4–8 years	**1.7 L/day of *total* water. This includes approximately 1.2 L (≈ 5 cups) as total beverages, including drinking water.**
AI for Boys	
9–13 years	**2.4 L/day of *total* water. This includes approximately 1.8 L (≈ 8 cups) as total beverages, including drinking water.**
14–18 years	**3.3 L/day of *total* water. This includes approximately 2.6 L (≈ 11 cups) as total beverages, including drinking water.**
AI for Girls	
9–13 years	**2.1 L/day of *total* water. This includes approximately 1.6 L (≈ 7 cups) as total beverages, including drinking water.**

[5] Conversion factors: 1 L = 33.8 fluid oz; 1 L = 1.06 qt; 1 cup = 8 fluid oz.

14–18 years **2.3 L/day of *total* water. This includes approximately 1.8 L (≈ 8 cups) as total beverages, including drinking water.**

Adults Ages 19 Through 50 Years

Evidence Considered in Setting the AI

Hydration status, as assessed by plasma or serum osmolality, is the primary indicator used for water. As documented previously, physical activity and environmental conditions have substantial influences on water needs (see later section, "Special Considerations"). Also, because of homeostatic responses, some degree of over- and underhydration can readily be compensated over the short-term. While it might appear useful to estimate an average requirement (an EAR) for water, it is not possible. An EAR is set based on data indicating that about half the individuals in the life stage group would have their needs met, while the other half would be inadequate at a specific intake level. Given the extreme variability in water needs that are not solely based on differences in metabolism, but also in environmental conditions and activity, there is not a single level of water intake that would ensure adequate hydration and optimal health for half of all apparently healthy persons in all environmental conditions. Thus an AI is established in place of the EAR (upon which a Recommended Dietary Allowance could be based).

Based upon a review of water balance studies (Table 4-5) for inactive adults in temperate climates, the minimal water requirement should be approximately 1 to 3.1 L/day to replace respiratory, urinary, fecal, and insensible fluid losses (Table 4-2). Data from NHANES III demonstrate that normal hydration status for all adults, as measured by serum osmolality, can be achieved with a wide range of water intakes (e.g., first through 99th percentile of total water intake) (Appendix Table G-1). Therefore, the AIs for *total* water are set based on median intakes of *total* water (drinking water, beverages, and food) from NHANES III (Appendix Table D-1), rounded to the nearest 0.1 L. These AIs cover the minimal losses that routinely occur in temperate climates for somewhat sedentary individuals and are based upon the factors previously discussed.

Individual water requirements can vary greatly, even on a day-to-day basis, because of differences in physical activity and climates. To a lesser extent, dietary factors also influence water requirements, as the osmotic load created by metabolizing dietary protein and or-

ganic compounds, as well as by varying intakes of electrolytes, must be accommodated by adequate *total* water consumption. Hence there is no single daily *total* water requirement for a given person, and need varies markedly depending primarily on physical activity and climate, but also based on diet. It would be misinterpreting the basis for setting the AI to state that there is a "requirement" for water at the level of the AI. As is discussed in Chapter 1, the AI does not represent a requirement; it is an amount that should meet the needs of almost everyone in the specific life stage group under the conditions described. It is thus determined on a different scientific basis than other recommendations for water or fluid intake (NRC, 1989).

The AI for *total* water intake for young men and women (19 to 30 years) is 3.7 L (131 oz) and 2.7 L (95 oz)/day, respectively, which correspond to median intakes for this age group in the NHANES III survey (Appendix Table D-1). Fluids (drinking water and beverages) provided about 3.0 and 2.2 L/day for 19- to 30-year-old men and women, respectively, representing approximately 81 percent of *total* water intake (Appendix Table D-3). Water from food provided 19 percent of *total* water intake, or 0.7 L/day for men and 0.5 L/day for women (Appendix Table D-4). While it is recognized that the median intake for men and women 31 to 50 years was lower, there is no reason to assume that the level recommended for adults 19 to 30 years would be in excess. Therefore, the AI for those ages 31 to 50 years is set equal to that for younger adults.

It is recognized that nationwide surveys such as NHANES III that rely on self-report are often inaccurate and possibly biased, with a greater tendency to underestimate actual intake (IOM, 2001b). People who meet the recommended 60 minutes per day or the equivalent of moderate physical activity (IOM, 2002/2005) and consume approximately 2,200 kcal can meet the AI through beverages and food (see Table 4-14).

Total Water AI Summary, Ages 19 Through 50 years

AI for Men	
19–30 years	**3.7 L/day of *total* water. This includes approximately 3.0 L (≈ 13 cups) as total beverages, including drinking water.**[6]
31–50 years	**3.7 L/day of total water. This includes approximately 3.0 L (≈ 13 cups) as total beverages, including drinking water.**

[6] Conversion factors: 1 L = 33.8 fluid oz; 1 L = 1.06 qt; 1 cup = 8 fluid oz.

TABLE 4-14 Daily Water Intake from a Diet Providing 2,200 kcal

Meal	Food/Beverage Consumed	Energy (kcal)	Water (mL)
Breakfast	Shredded wheat miniatures fortified ready-to-eat cereal (1 cup)	183	2
	Milk, 1% (8 oz)	102	219
	Orange juice (6 oz)	82	165
	Cantaloupe, cubed (½ cup)	27	72
	White toast (1 slice) with unsalted margarine vegetable oil spread (1 tsp)	89	9
	Coffee, black, unsweetened (12 oz.)	13	354
	Total for meal	**496**	**821**
Snack	Banana (1 medium)	105	88
	Water (12 oz.)	0	356
	Total for snack	**105**	**444**
Lunch	Sandwich with turkey (2 oz) Swiss cheese (1 oz), lettuce (2 leaves), tomato (¼″ slice), and mayonnaise (1 tbsp) on whole wheat bread (2 slices)	395	113
	Baby carrots (8)	28	72
	Fig bars cookies (2)	111	5
	Iced tea, brewed, decaffeinated (16 oz)	5	472
	Total for meal	**539**	**662**
Snack	Almonds, dry roasted, unsalted (¼ cup)	206	1
	Raisins (¼ cup)	108	6
	Milk, 1% (8 oz)	102	219
	Water (12 oz)	0	356
	Total for snack	**416**	**582**
Dinner	Baked salmon (3 oz)	151	57
	Long-grain brown rice (½ cup cooked)	108	71
	Tossed salad (1½ cups) with safflower oil and vinegar dressing (2 tbsp)	155	212
	Asparagus (6 spears)	20	83
	Wheat roll (1 medium) with unsalted margarine vegetable oil spread (1 tsp)	101	12
	Angel food cake (1 slice) with sliced strawberries (½ cup) and whipped cream topping (2 tbsp)	114	88

TABLE 4-14 Continued

Meal	Food/Beverage Consumed	Energy (kcal)	Water (mL)
	Iced tea, brewed, decaffeinated (16 oz)	5	472
	Coffee, black, unsweetened, decaffeinated (8 oz)	9	236
	Total for meal	**663**	**1,231**
	Total water from food		891
	Total water from beverages		2,849 (≈ 12 cups)
	Daily total	**2,219 kcal**	**3,740**

NOTE: This diet meets the Adequate Intake or the Recommended Dietary Allowance for adult men and women for all nutrients for which one has been established (for fiber, it meets the ratio of 14 g/1,000 kcal) and provides energy nutrients within the acceptable macronutrient distribution ranges. Nutrient totals may not equal the sum of the parts, due to rounding. Vegetables prepared without salt.
Food composition data: U.S. Department of Agriculture, Agricultural Research Service, Nutrient Database for Standard Reference, Release 16.
DATA SOURCE: ENVIRON International.

AI for Women

19–30 years **2.7 L/day of total water. This includes approximately 2.2 L (≈ 9 cups) as total beverages, including drinking water.**

31–50 years **2.7 L/day of total water. This includes approximately 2.2 L (≈ 9 cups) as total beverages, including drinking water.**

Older Adults and the Elderly Ages 51+ Years

Evidence Considered in Setting the AI

Renal Concentrating Ability. Renal concentrating ability is well known to decline with age in humans (Dontas et al., 1972; Lindeman et al., 1966; Rowe et al., 1976). In several studies the maximal urine osmolality, when measured following 12 to 24 hours of dehydration, was inversely related to age (Dontas et al., 1972; Lindeman et al., 1966). In one study, the maximal urine osmolality was 1,109 mOsmol/kg in 31 subjects 20 to 39 years old, compared with 1,051 mOsmol/kg in 48 subjects 40 to 59 years old and 882 mOsmol/kg in 18 subjects 60 to 79 years old (Rowe et al., 1976). It is interesting to note that the age-related decline in concentrating

ability did not correlate with the age-related decline in the glomerular filtration rate (GFR) (Dontas et al., 1972; Rowe et al., 1976). While this age-related deficit in water conservation can easily be demonstrated in physiologic studies, it is likely to be of major clinical consequence if individuals are exposed to high solute excretion requirements.

Studies in humans suggest that the concentrating defect is due to an intrarenal defect rather than a failure in the osmotic-induced release of arginine vasopressin (Helderman et al., 1978; Lindeman et al., 1966; Miller and Shock, 1953). Following intravenous infusion of hypertonic saline (3 percent sodium chloride) in eight young (22 to 48 years of age) and eight older (52 to 66 years of age) men, serum arginine vasopressin concentrations rose 4.5 times the baseline in the older men compared with 2.5 times the baseline in the younger men despite similar free water clearances (Helderman et al., 1978). The slope of the serum arginine vasopressin concentration (as a percentage of baseline) versus serum osmolality, an index of the sensitivity of the osmoreceptor, was significantly increased in the older subjects. In addition, intravenous infusion of ethanol in 9 younger (21 to 49 years of age) and 13 older (54 to 92 years of age) men resulted in a progressive decline in plasma arginine vasopressin levels in the young subjects, but failed to have a similar effect in the older subjects (Helderman et al., 1978).

In contrast to osmotic stimulation, volume-pressure-mediated arginine vasopressin release has been found to decrease with old age and appears to be absent in many healthy elderly people (Rowe et al., 1982). An additional factor that may influence arginine vasopressin concentrations and impair water conservation in the elderly is the increase in atrial natriuretic peptide (ANP) concentrations with age, since ANP has been demonstrated to suppress arginine vasopressin release in response to hyperosmolality in young and old individuals (Clark et al., 1991).

Studies in humans reveal an age-related increase in solute excretion and osmolar clearance during dehydration (Rowe et al., 1976). This phenomenon, which may be a reflection of an impaired solute transport by the ascending loop of Henle, may be responsible for the impairment in urine concentrating ability in elderly subjects. This possibility is supported by clearance studies during water diuresis that demonstrate a decrease in the sodium chloride transport in the ascending loop of Henle in elderly subjects (Macias-Nunez et al., 1978, 1980). This defect in solute transport by the thick ascending limb of the loop of Henle could diminish inner medullary hypertonicity and thereby impair urinary concentrating ability.

Renal Diluting Ability

Renal diluting ability is also impaired as a function of aging (Crowe et al., 1987; Epstein, 1985; Lindeman et al., 1966). In water-diuresing subjects as a result of water loading, minimal urine osmolality was significantly higher: 92 mOsmol/kg in the elderly subjects (aged 77 to 88 years) when compared with 52 mOsmol/kg in the young subjects (aged 17 to 40 years). Free water clearance was also decreased: 5.9 mL/minute in the elderly subjects compared with 16.2 mL/minute in the young subjects (Lindeman et al., 1966). While the impairment is largely due to the decrease in GFR, when free water clearance is factored for GFR, the ratio of free water clearance to GFR is, however, still decreased in the older subjects (Crowe et al., 1987; Lindeman et al., 1966). Mechanisms of the impaired diluting ability in the elderly have not been well studied. In addition to the major role of impaired GFR, inadequate suppression of arginine vasopressin release or impaired solute transport in the ascending loop of Henle may also play a role.

Thirst in the Elderly

The age-related impairments in renal-concentrating and sodium-conserving ability are associated with an increased incidence of volume depletion and hypernatremia in the elderly (Snyder et al., 1987). Under normal physiological conditions, increased thirst and fluid intake are natural defense mechanisms against volume depletion and hypernatremia. A deficit in thirst and regulation of fluid intake in the elderly, however, may further contribute to the increased incidence of dehydration and hypernatremia.

Several studies confirm the long-held clinical observation that thirst and fluid intake are impaired in the elderly (Fish et al., 1985; Miller et al., 1982; Murphy et al., 1988; Phillips et al., 1984). In a series of studies the osmotic threshold for thirst during hypertonic saline infusion has been found to be much higher in healthy elderly subjects than in their younger counterparts, with many apparently healthy elders not reporting thirst despite elevations of plasma osmolality to levels over 300 mOsmol/kg (Fish et al., 1985). In studies of water ingestion after intravenously induced hyperosmolality, elderly individuals demonstrated marked reductions in their water intake and rate of return of plasma osmolality to baseline when compared with the younger group (Murphy et al., 1988). The influence of free access to water on prevention of serum osmolality increases during hypertonic saline infusion was also investigated (McAloon-

Dyke et al., 1997). Despite equivalent increases in plasma volume, the older group consumed significantly less water and had greater increases in serum osmolality than the younger group.

Thirst may also be severely impaired in patients with a prior history of stroke who do not have cognitive impairment or evidence of hypothalamic or pituitary dysfunction (Miller et al., 1982). The complication of age-related decreases in thirst by systemic illnesses and dementia in many frail elderly patients clearly place them at risk for the development of severe water deficiency.

Summary. While there are differences in renal physiology that occur with aging, Appendix Table G-1 (which provides serum osmolality values by percentile of water intake) indicates that hydration status continues to be normal over a wide range of intakes for elderly individuals as well as younger individuals. The AI for total water (drinking water, beverages, and foods) for the elderly is set based on median total water intake of young adults (Appendix Table D-1), rather than the older age group, in order to ensure that total water intake is not limited in the face of a potential declining ability to consume adequate amounts in response to thirst.

Total Water AI Summary, Ages 51+ Years

AI for Men	
51–70 years	**3.7 L/day of total water. This includes approximately 3.0 L (≈ 13 cups) as total beverages, including drinking water.**[7]
> 70 years	**3.7 L/day of total water. This includes approximately 3.0 L (≈ 13 cups) as total beverages, including drinking water.**
AI for Women	
51–70 years	**2.7 L/day of total water. This includes approximately 2.2 L (≈ 9 cups) as total beverages, including drinking water.**
> 70 years	**2.7 L/day of total water. This includes approximately 2.2 L (≈ 9 cups) as total beverages, including drinking water.**

[7] Conversion factors: 1 L = 33.8 fluid oz; 1 L = 1.06 qt; 1 cup = 8 fluid oz.

Pregnancy

Evidence Considered in Setting the AI

Body Water. Weight increases about 12 kg during an average pregnancy, but approximately 15 percent of normal pregnant women also develop generalized swelling and additional weight gain (≈ 2.5 kg) (Chesley, 1978; Forsum et al., 1988; Hytten, 1980; Hytten and Leitch, 1971; Lindheimer and Katz, 1985). Most of this added weight is water and includes the products of conceptus and gains within the expanded maternal intra- and extracellular spaces.

Total body water has been measured during gestation with deuterium, the stable isotope of oxygen, or by bioelectric impedance (Catalano et al., 1995; Chesley, 1978; Forsum et al., 1988; Hytten, 1980; Hytten and Leitch, 1971; Lindheimer and Katz, 1985). Results vary (due partly to different methodologies, but also to the period of testing with interpolation from final measurement until term), with findings of total accumulation from 6 to 9 L, of which 1.8 to 2.5 L are intracellular fluid. The increases in maternal vascular and interstitial volumes are discussed in Chapter 6, and further discussions of the validity of methodologies utilized primarily in studies of the extracellular-extravascular compartment are discussed by Chesley (1978) and Lindheimer and Katz (1985, 2000).

Hydration Status and Plasma Osmolality. Plasma osmolality decreases by 8 to 10 mOsmol/kg during normal gestation. The decrement that normally starts during the luteal phase of the menstrual cycle continues through conception, reaching its lowest point during gestational week 10, after which the decline is sustained until term (Davison et al., 1981, 1984; Lindheimer and Davison, 1995). Since only approximately 1.5 mOsmol/kg of the decrease can be attributed to the small decrement in circulating urea, most of the decline is due to lower levels of sodium and its attendant anion. Thus gestation is characterized by a decrease in body tonicity (i.e., effective osmolality). The reason for this decline is a parallel decrease in the osmotic thresholds for arginine vasopressin release and thirst, with the pregnant woman then concentrating and diluting urine appropriately around this new steady-state body tonicity (Davison et al., 1981; Lindheimer and Davison, 1995). Since the threshold for arginine vasopressin release decreases a bit more rapidly than that for thirst, pregnant women may experience a short transient period of polyuria during early gestation (Davison et al., 1988).

When stressed by dehydration or water loading, pregnant women respond in a manner similar to that of nonpregnant women, in spite of the large increase in glomerular filtration rate that accompanies gestation, which might increase filtered solute substantially and thus compromise the extremes of concentration and dilution.

The metabolism of arginine vasopressin is markedly altered during pregnancy as metabolic clearance rate increases fourfold between early and mid-gestation (Davison et al., 1989, 1993). This is due to the appearance of high circulating levels of placental vasopressinase (a cystine aminopeptidase). Normally the production rate of arginine vasopressin is sufficient to overcome the increased disposal rate, but there are rare instances of subclinical central diabetes insipidus that become apparent by the increased metabolic clearance rate of arginine vasopressin in pregnancy (Baylis et al., 1986; Lindheimer and Davison, 1995). There are also instances of overproduction of vasopressinase resulting in a syndrome-labeled transient diabetes insipidus during pregnancy (Durr et al., 1987; Lindheimer and Davison, 1995).

Summary. While there are differences in plasma osmolality during pregnancy, the differences are not a result of poor hydration status and are short term. Therefore, an AI for total water (drinking water, beverages, and food) during pregnancy is based on the estimated median total water intake during pregnancy (Appendix Table D-1). In the NHANES, water from food provided 22 percent of the estimated total water intake, slightly more than the 19 percent of the estimated total water consumption seen in nonpregnant women (Appendix Table D-4).

Total Water AI Summary, Pregnancy

AI for Pregnancy	
14–18 years	**3.0 L/day of total water. This includes approximately 2.3 L (≈ 10 cups) as total beverages, including drinking water.**[8]
19–30 years	**3.0 L/day of total water. This includes approximately 2.3 L (≈ 10 cups) as total beverages, including drinking water.**
31–50 years	**3.0 L/day of total water. This includes approximately 2.3 L (≈ 10 cups) as total beverages, including drinking water.**

[8] Conversion factors: 1 L = 33.8 fluid oz; 1 L = 1.06 qt; 1 cup = 8 fluid oz.

Lactation

Evidence Considered in Setting the AI

There is no evidence to suggest that renal function and hydration status are different during lactation. Therefore, the AI for *total* water (drinking water, beverages, and food) is set based on median *total* water intakes during lactation estimated in the NHANES III (Appendix Table D-1). In this survey, water from food for this life stage group was estimated to provide 19 percent of *total* water intake (Appendix Table D-4).

Another approach to determining the *total* water needs during lactation would be to sum the nonpregnant AI (2.3, 2.7, and 2.9 L/day for 14- through 18-, 19- through 30-, and 31- through 50-year-old females, respectively) and the water content of the average milk output during the first 6 months of lactation (0.78 L milk × 87 percent = 0.68 L water). This generates an estimated *total* water intake of 3.0, 3.4, and 3.6 L/day for lactating females 14 to 18, 19 to 30, and 31 to 50 years of age, respectively. These estimates closely coincide with the AI for *total* water based on median intake during lactation. Hence, the latter, median intake during lactation is used as the AI for all age groups.

Total Water AI Summary, Lactation

AI for Lactation	
14–18 years	**3.8 L/day of *total* water. This includes approximately 3.1 L (≈ 13 cups) as total beverages, including drinking water.**[9]
19–30 years	**3.8 L/day of *total* water. This includes approximately 3.1 L (≈ 13 cups) as total beverages, including drinking water.**
31–50 years	**3.8 L/day of *total* water. This includes approximately 3.1 L (≈ 13 cups) as total beverages, including drinking water.**

[9] Conversion factors: 1 L = 33.8 fluid oz; 1 L = 1.06 qt; 1 cup = 8 fluid oz.

Special Considerations

Active Adults

Physical activity and environmental exposure will increase water losses and therefore increase daily fluid needs. Physically active persons are often more likely to be outdoors and exposed to ambient environmental conditions (e.g., hot weather). Because dehydration will reduce physical exercise capabilities and increase heat strain (e.g., body temperature), it is important that active populations adequately replace their fluid losses (IOM, 1994; Sawka and Coyle, 1999).

As previously discussed, this increased water loss is essentially equal to sweat losses, as increased respiratory water losses are essentially offset by increased production of metabolic water. Water balance studies (Table 4-5) indicate that going from minimal activity to sedentary activity levels in temperate environments increased daily water requirements from approximately 2.5 to 3.2 L/day, respectively. Water turnover studies (Table 4-6) indicate that individuals with more strenuous levels of activity (> 60 minutes per day of activity) compared with individuals engaging in relatively sedentary activity (i.e., less than 60 minutes per day of activity) in temperate environments have increased daily total water requirements of approximately 3.0 to 4.5 L/day in men (Fusch et al., 1998; Leiper et al., 1996). Higher levels of physical activity further increase water requirements; for example, very active fire fighters had daily water requirements of about 7 L/day (Ruby et al., 2002).

Data from NHANES III (Table 4-15; Appendix H) indicate that individuals reporting leisure time activity five or more times per week had higher median daily water intakes by ≈ 0.5 L/day (e.g., 19 to 30 years: men 3.16 to 3.78 L/day, women 2.60 to 2.93 L/day). If persons perform physical activity in hot weather, then daily water requirements will be markedly increased. For active populations living in tropic or desert weather, daily sweat losses are often an additional 2 to 7 L/day (IOM, 1993, 1994; Molnar, 1947). Several analyses of water losses in hot weather (Figures 4-16, 4-17, and 4-18) support that active individuals who are continually exposed to hot weather can often have daily water requirements of 6 to 8 L/day or more.

Figure 4-20 provides approximate daily fluid requirements based on modeling for adults (assuming approximately 1.0 L for minimal needs for urine, respiratory, gastrointestinal, and insensible losses [Table 4-2]) wearing light-weight clothing while exposed to a vari-

TABLE 4-15 Summary of Estimated Median Daily Total Water Intake for Individuals Reporting Leisure Time Activity in the United States

	Males, Total Water Intake (L/d)		Females, Total Water Intake (L/d)	
Age	Least Active,[a] Median	Most Active,[b] Median	Least Active,[a] Median	Most Active,[b] Median
8–16 yr	2.11	2.69	1.78	2.29
17–18 yr	2.04	3.35	1.90	2.74
19–30 yr	3.16	3.78	2.60	2.93
31–50 yr	3.54	3.77	2.52	3.16
51–70 yr	3.22	3.42	2.81	3.06
71+ yr	2.54	3.05	2.33	2.75

[a] Least active = no reported leisure time activity.

[b] Most active = leisure time activity reported five or more times per week.

SOURCE: Third National Health and Nutrition Examination Survey, 1988–1994. Appendix Tables H-1, H-2, and H-4.

ety of average daytime ambient dry bulb temperatures (i.e., with 50 percent relative humidity and a partly cloudy sky) and varying their level of physical activity from sedentary, low active, active, and very active levels. The sweating rates were predicted by an equation developed for healthy adults that includes the effects of metabolic rate, climate, and clothing (Moran et al., 1995; Sawka et al., 1996a; Shapiro et al., 1982). Considerable variability can be expected among persons due to individual differences in body size, diet, and sweat loss responses (e.g., heat acclimatization, physical fitness, air movement). In addition, most individuals will not be constantly exposed to one environmental condition. Note that the daily water requirements for temperate conditions can double or even triple in very hot weather (≈ 40°C [104°F]). Adolph's (1933) "minimal," "average," and "liberal" water requirements of 2.1, 3.4, and 5.0 L/day, respectively, are fairly consistent with this figure, except for very active persons in hot weather. The daily water requirement increases with activity and ambient temperature are a result of increased sweating to meet evaporative cooling requirements.

Active Children

Sweat production in children is considerably less than in adults under similar climatic and activity conditions (Falk, 1998). This dif-

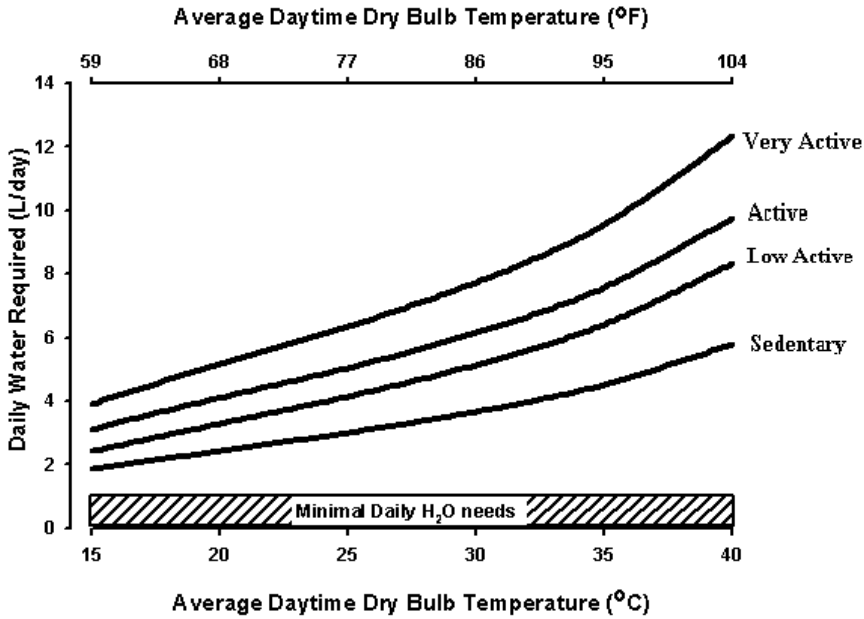

FIGURE 4-20 Approximate daily sweating rates as a function of dry-bulb temperature and level of physical activity derived from modeling available data. The hatched area indicates the ≈ 1 L minimal water requirements as described in Table 4-2. The y-axis represents the predicted water requirements that increase because of increased sweat losses to enable thermoregulation. The x-axis is the average daytime dry bulb temperature. "Very active" is equivalent to approximately 3,600 total kcal/day of energy expenditure, "active" is equivalent to approximately 2,900 total kcal/day of energy expenditure, "low active" is equivalent to approximately 2,400 total kcal/day of energy expenditure, and "sedentary" is equivalent to approximately 1,900 total kcal/day of energy expenditure, categories identified in estimates of energy expenditure (IOM, 2002/2005). The model used to develop this graph is further explained in Appendix C.

ference prevails even when sweating rate is corrected for skin surface area (Araki et al., 1979; Falk et al., 1992a; Wagner et al., 1972), and it becomes manifested during midpuberty. For example, while performing moderate-intensity exercise at dry climatic heat (42°C [107.6°F], 20 percent relative humidity), prepubertal boys produced ≈ 15 to 25 percent less sweat, 294 mL/m^2skin/hour of sweat compared with 342 and 396 mL/m^2skin/hour in mid- and late-pubertal boys, respectively (Falk et al., 1992b).

Similar to the adult considerations for those exposed to climatic heat stress, the above differences should be taken into consideration when determining water requirements of active children and adolescents. They are unimportant for sedentary or mildly active young people not exposed to climatic heat who therefore produce little or no sweat.

INTAKE OF WATER

Sources

Sources of water consumed to meet body needs include beverages, food, and drinking water. Although water is thought of as the primary fluid to sustain hydration, fluids in different types of beverages and foods contribute significantly to a person's daily fluid needs (Heller et al., 1999; Appendix Tables D-1, D-2, D-3, and D-4). Figure 4-21 shows the sources and quantities of water consumed as

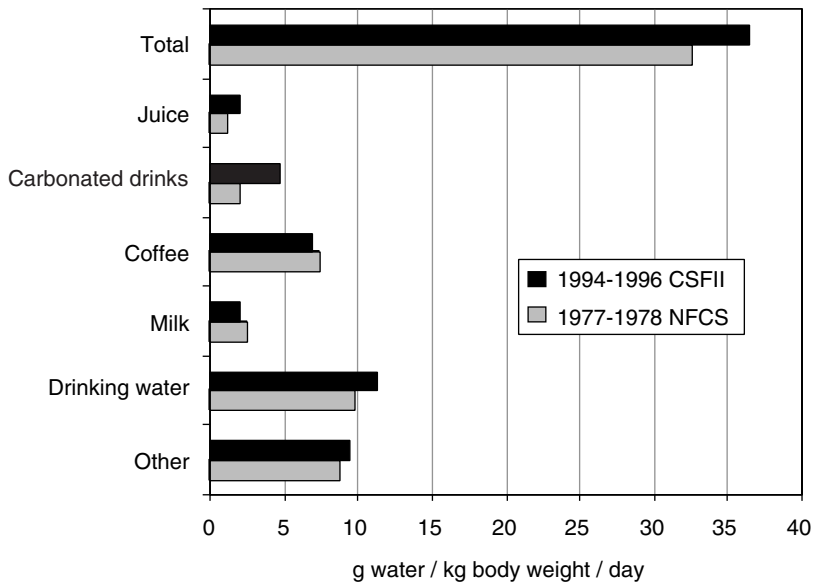

FIGURE 4-21 Sources and quantities of beverage intake for individuals aged 20 to 64 years as provided by the 1977–1978 National Food Consumption Survey (NFCS) and 1994–1996 Continuing Survey of Food Intakes by Individuals (CSFII). Reprinted with permission, from Heller et al. (1999). Copyright 1999 by the American Association of Public Health Dentistry.

TABLE 4-16 Water Content of Selected Foods

Food	Water (% wt)	Food	Water (% wt)
Apple, raw	86	Ham, cooked	70
Apricot, raw	86	Lettuce, iceberg	96
Banana, raw	75	Macaroni/spaghetti, cooked	66
Bread, white	36	Milk, 2%	89
Bread, whole-wheat	38	Orange, raw	87
Broccoli, cooked	89	Peach, raw	89
Cantaloupe, raw	90	Peanuts, dry roasted	2
Carrots, raw	88	Pear, raw	84
Cheese, cheddar	37	Pickle	92
Cheese, cottage	79	Pineapple, raw	86
Chicken, roasted	64	Potato, baked	75
Chocolate chip cookies	4	Squash, cooked	94
Corn, cooked	70	Steak, tenderloin, cooked	50
Corn flakes cereal	3	Sweet potato, boiled	80
Crackers, saltines	4	Turkey, roasted	62
Grapes, raw	81	Walnuts	4

SOURCE: USDA/ARS (2002).

fluid by individuals 20 to 64 years old as provided by the 1977–1978 Nationwide Food Consumption Survey and the 1994–1996 Continuing Survey of Food Intakes by Individuals (CSFII) (Heller et al., 1999). Table 4-16 shows the water content of various foods. Fruits and vegetables contain a high percentage of water. For adults in the United States, drinking water provided 35 to 54 percent of total water, while foods and beverages provided 19 to 25 percent and 49 to 63 percent, respectively (Appendix Tables D-1, D-2, D-3, and D-4). Together, drinking water and beverages provided 73 to 80 percent of the total water consumed as food and fluids. Analysis of other data (Ershow and Cantor, 1989) showed total water intake with approximately 28 percent coming from food, 28 percent from drinking water, and 44 percent from other beverages. Foods such as soup and ice cream were included in the food category.

Intake

Appendix D, using data from the Third National Health and Nutrition Examination Survey (NHANES III), provides the daily intake of water from (1) total sources (food and beverages), (2) drinking water, (3) drinking water and beverages, and (4) foods. Table 4-17

TABLE 4-17 Daily Estimated *Total* Water Intake of Infants and Young Children in the United States

		Total Water Intake[a] (L)				*Total* Water Intake (L/kg body weight)	
Age	*n*	Mean	Median	5th Percentile	95th Percentile	Mean	Median
2–6 mo	780	1.11	1.05	0.61	1.79	0.152	0.145
7–12 mo	807	1.32	1.26	0.77	2.03	0.144	0.137
1–3 yr	3,142	1.42	1.32	0.70	2.49	0.107	0.099
4–8 yr	3,225	1.78	1.74	1.24	2.45	0.079	0.077

[a] *Total* water intake reflects the sum of plain drinking (tap) water and the water content of all foods, formula, and beverages consumed.

NOTE: Data are limited to individuals who provided a valid response to the question, "How much plain drinking water do you usually drink in a 24-hour period? Include only plain tap or spring water" and provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method to provide estimates of usual intake. Means and medians were obtained using C-Side. Infants and children fed human milk were excluded from the analysis.

DATA SOURCE: Appendix Table D-1: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics (2003).

summarizes the medians and ranges of water intake of infants and young children of both genders. Note that with maturation, the range of total water (difference between the 5th and 95th percentiles) increases. The expanding range probably results from differences in body size, physical activity, and environmental exposure.

Table 4-18 summarizes the median values of *total* water intake (food and beverages) for male and female older children, adolescents, and adults in the United States (Appendix D). Daily total water intake values are lower in females than in males at all ages. For both genders, daily total fluid intakes are relatively constant from late teens to late middle age, with slightly lower values before and after. The variability of values is probably not due to altered hydration status, as serum osmolalities are similar (and indicative of euhydration) across age groups and deciles of total water intake (see earlier section, "Plasma Indicators," and Appendix G). Women

TABLE 4-18 U.S. Estimated Daily *Total* Water Intake of Male and Female Older Children, Adolescents, and Adults

	Males, *Total* Water Intake[a] (L/d)			Females, *Total* Water Intake (L/d)		
Age	Mean	Median	5th to 95th Percentiles	Mean	Median	5th to 95th Percentiles
9–13 yr	2.54	2.44	1.50–3.90	2.24	2.13	1.27–3.58
14–18 yr	3.40	3.28	2.12–5.09	2.50	2.33	1.27–4.30
19–30 yr	3.91	3.71	2.26–6.23	2.84	2.69	1.40–4.80
31–50 yr	3.85	3.63	2.10–6.34	3.10	2.90	1.59–5.28
51–70 yr	3.55	3.39	2.02–5.64	3.02	2.90	1.65–4.83
71+ yr	2.99	2.90	1.77–4.56	2.62	2.54	1.54–3.97

[a] *Total* water intake reflects the sum of plain drinking (tap) water and the water content of all foods, formulas, and beverages consumed.

DATA SOURCE: Appendix Table D-1: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics (2003).

had lower (relative to men) total water intake values by approximately 0.4 L/day early and late in life and by approximately 1.0 L/day from 14 to 30 years of age. Differences in daily total water intake are probably somewhat due to differences in body size, physical activity, and climatic exposure.

Table 4-19 summarizes the total intake for moisture (water content from foods and beverages) in the Canadian Provincial survey 1990–1999 (Appendix Table F-1). They are somewhat lower than the estimates from the NHANES for individuals in the United States. However, similar trends are seen to that seen with the U.S. data: intake of females is lower on average for all adult age groups, and water intake as estimated by moisture remains relatively constant through adulthood, declining in the oldest age group (71+ years of age).

Table 4-15 summarizes the daily total water intake from the NHANES in the United States (from all sources—food and beverages) for the least active (reported no leisure activity during the week) and most active (leisure activity reported five or more times per week) persons surveyed (Appendix H). These data do not represent the water requirements for a specific metabolic rate, but rather the total water intake on a given day (whether or not the

TABLE 4-19 Canadian Daily *Total* Moisture (Water from Food and Beverages) Intake for Men and Women

	Men, *Total* Water Intake (L/d)			Women, *Total* Moisture Intake (L/d)		
Age	Mean	Median	5th to 95th Percentiles	Mean	Median	5th to 95th Percentiles
19–30 yr	3.04	2.69	1.74–4.40	2.46	2.23	1.31–3.98
31–50 yr	2.96	2.71	1.90–4.47	2.55	2.38	1.50–3.67
51–70 yr	2.71	2.52	1.57–4.10	2.41	2.24	1.46–3.58
71+ yr	2.39	2.31	1.57–3.39	2.14	2.06	1.38–3.20

SOURCE: Appendix Table F-1; Health Canada.

individual participated in leisure activity that day). It is reasonable to assume that these two populations differed in physical activity levels on the surveyed day; however, data are not available to document this difference. The more active groups had a greater daily total water intake by approximately 0.6 and 0.5 L for the men and women, respectively.

There are few data concerning water intake during gestation or during lactation. NHANES III surveyed 341 pregnant and 98 lactating women (Appendix D). The median daily intake of drinking and beverage water was estimated to be 2.3 L, and the intake of water from food was 0.6 L, providing a total intake of approximate 2.9 L for total water from foods, beverages, and drinking water. CSFII surveyed 124 women listed as pregnant or lactating (Appendix E). The median daily intake of drinking and beverage water was estimated to be 1.8, and the intake of water from food was 0.7, providing a total water intake of approximately 2.5 L from foods, beverages, and drinking water. CSFII data were not separated as to period of gestation nor to gestation versus lactation.

ADVERSE EFFECTS OF OVERCONSUMPTION

Water intoxication can lead to hyponatremia, which can be life threatening. This occurs occasionally in psychiatric patients (psychogenic polydipsia) and needs to be addressed quickly before serious side effects occur. Water intoxication and death from acute water toxicity have also been reported in nonpsychiatric situations in which voluntary consumption of excess amounts occurred

(Gardner and Gutmann, 2002), as well as in other social situations in which excess fluid ingestion was involved (Arieff and Kronlund, 1999). Hyponatremia can also occur from excessive fluid intake, under-replacement of sodium, or both during or after prolonged endurance athletic events. Hyponatremia is rare in healthy populations consuming the average North American diet.

Psychogenic polydipsia is the excessive consumption of fluid, especially water, among chronic psychiatric patients, but particularly those with schizophrenia (de Leon et al., 1994). This concept has been known since 1935 (Sleeper, 1935); however, it is still poorly understood. There have been a number of case studies published (Adler, 1980; Akasaki et al., 1993; Browne, 1979; de Leon et al., 1994; Gehi et al., 1981; Jos et al., 1986; Koczapski and Millson, 1989; Korzets et al., 1996; Ledochowski et al., 1986; Mor et al., 1987; Okura et al., 1990; Sidi et al., 1984; Tomiyama et al., 1990; Yonemura et al., 1987) on psychogenic polydipsia and water intoxication, leading to hyponatremia and rhabdomyolysis, an injury to skeletal muscle tissue that results in the destruction of skeletal muscle cells and allows for the escape of cellular contents into the extracellular fluid, leading to renal failure and compartment syndromes (Korzets et al., 1996). Electroencephalographic changes have been reported with water intoxication in some patients (Okura et al., 1990).

Acute water toxicity has been reported due to rapid consumption of large quantities of fluids that greatly exceeded the kidney's maximal excretion rate of from 0.7 to 1.0 L/hour.

Hazard Identification

Hyponatremia is defined by a serum sodium level of less than 135 mmol/L, but symptoms are usually not apparent unless the serum sodium level is less than 130 mmol/L. The signs and symptoms of hyponatremia depend upon the rapidity with which the serum sodium declines, as well as on the absolute levels. The lowering of the extracellular fluid (ECF) sodium concentration causes fluid to move to the intracellular fluid (ICF) space, resulting in central nervous system edema, lung congestion, and muscle weakness.

Hyponatremia is very difficult to achieve in healthy persons consuming an average U.S. diet. As discussed previously, urine output will increase (and be dilute) in proportion to the excess fluid intake to reestablish water balance (Freund et al., 1995; Habener et al., 1964). Hyponatremia from excess fluid intake is most often observed in infants (Keating et al., 1991), and is also seen in psychiatric pa-

tients with polydipsia (de Leon et al., 1994), patients on psychotropic drugs (Siegel et al., 1998), women who have had operations using a uterine distension medium (Kim et al., 1995), individuals participating in prolonged endurance events (Montain et al., 2001; Noakes, 2002), and military recruits (O'Brien et al., 2001). Hyponatremia can sometimes lead to death (Gardner, 2002; Garigan and Ristedt, 1999). The U.S. Army has provided epidemiologic data for the incidence of hyponatremia hospitalizations for soldiers. The hyponatremia incidence rate averaged less than 1 per 100,000 soldier years, which was much less (35 to 70 times less frequent) than heat casualty hospitalizations (U.S. Army, 2003).

Increased total body water, which dilutes the ECF sodium, occurs from overconsumption of water. The misdiagnosis of hyponatremia as dehydration (as both share several symptoms) that is inappropriately treated with aggressive rehydration treatment (O'Brien et al., 2001) can worsen the hyponatremia. Likewise, a failure to excrete excess volume can exacerbate this condition. Hospitalized patients who develop hyponatremia may have impaired renal water excretion, which is often associated with an inappropriate (relative to osmotic and volume status) secretion of arginine vasopressin during the fluid overload (Gibbs et al., 2002). Nausea is a stimulus for arginine vasopressin, common in hyponatremia, and may account for some of the reported inappropriate arginine vasopressin responses. Likewise, exercise and heat stress will both reduce urine output (see earlier sections), and if excessive overconsumption occurs with prolonged stressful exercise, hyponatremia may develop. The symptomatic hyponatremia of exercise is typically associated with greater than 6 hours of prolonged stressful exercise (Montain et al., 2001).

It has been suggested that persons with certain mutations of the cystic fibrosis transmembrane regulatory (CFTR) gene may be susceptible to hyponatremia (Leoni et al., 1995). There are greater than 800 variants of the CFTR gene that have been identified; many are seen in otherwise healthy people, but they may be associated with exceptionally high sweat sodium losses (Montain et al., 2001).

The increase in total body water (TBW) required to decrease serum sodium to 125 mmol/L from an elevated level of 140 mmol/L is approximately 5.1 L for a 70-kg man, depending on the extent of the exercise and heat strain. This can be calculated as follows: a 70-kg man, who would have a TBW volume of about 42 L, and an ECF volume of approximately 14 L, would have an extracellular sodium content of approximately 1,960 mmol (14 L ECF $\times$ 140 mmol/L). To dilute his serum sodium from 140 to 125 mmol/L, the ECF

would need to increase by 1.7 L to 15.7 L ([140 ÷ 125 mmol/L] × 14 L) and, assuming that the ECF and the TBW increases are in proportion due to osmotic equilibrium, the TBW would need to increase by approximately 5.1 L ([15.7 L ÷ 14 L] × 42 L = 47.1 L) to provide this additional 1.7 L to the ECF.

However, if this person had been exercising in a hot climate and losing sodium in sweat, then less overhydration (hypoosmotic fluid consumption) is required to reduce plasma sodium to 125 mmol/L, assuming sweat losses are replaced as well. If sweat losses total 6 L and sweat sodium concentration is 25 mmol/L (since it is less concentrated than serum), then there is a 150 mmol sodium deficit due to sodium loss (ECF sodium would be decreased to 1,810 mmol [1,960 mmol – 150 mmol]). If the 6-L water loss as sweat is replaced by sodium-free fluid, then the sodium deficit would produce a 3.6 mmol decrease to the TBW (150 mmol ÷ 42 L = 3.6 mmol/L) and effectively reduce ECF sodium to 136.4 mmol/L (140 – 3.6 = 136.4). The volume of excess fluid intake necessary to further dilute ECF sodium to 125 mmol/L would be 3.8 L ([136.4 ÷ 125 mmol/L] × 42 L), less than the 5.1 L needed to decrease hypernatremia from 140 mmol to 125 mmol/L where sweating had not occurred. Thus the total fluid intake would need to be 9.8 L (6 L [to replace that lost in sweat] + 3.8 L [needed to allow the TBW to be at equilibrium with the ECF]).

Smaller persons, such as women and children, are more susceptible to hyponatremia due to having smaller TBW and ECF volumes, therefore the same magnitude of overdrinking (as a larger person) dilutes a smaller osmotic content.

Bladder Lesions

The gross overconsumption of fluids (such as > 20 L/day) has been suggested as being associated with irreversible bladder lesions in a series of case studies (Susset, 1993). In addition, possible association of thinner bladder muscles, delayed bladder sensation, and flow rate impairment due to excessive fluid intake was suggested (Susset, 1993).

Dose-Response Assessment

While hazards associated with overconsumption can thus be identified, there are no data on habitual consumption of elevated water intakes resulting in identifiable hazards in apparently healthy people. Because of the significant ability to self-regulate excessive

consumption of water from fluids and foods by healthy people in temperate climates, a Tolerable Upper Intake Level was not set for water.

Intake Assessment

The highest (99th percentile of intake) total water intake reported was 8.1 L/day in men aged 31 to 50 years (Appendix Table D-1). Only 5 percent of men consumed in excess of 6.4 L/day of water.

Risk Characteristics

No adverse effects have been reported with chronic high intakes of water in healthy people consuming a normal diet, as long as fluid intake is approximately proportional to losses.

RESEARCH RECOMMENDATIONS

- Development of simple non- or minimally invasive indexes of body hydration status (both hyperosmotic and isoosmotic).
- Controlled water balance studies in different subgroups of the population (i.e., children, elderly, and those with chronic illnesses) in different climatic conditions.
- Development of capabilities to predict hourly and daily water requirements based on metabolic rate, climatic conditions, and clothing for different subgroups of the population.
- Studies in water consumption and retention patterns due to meal schedule and diet.
- Validation of estimates of total water intake, both from food and fluids, in large-scale surveys.
- Additional studies on the effects of water deficits on cognitive performance.
- The effects of water deficits on the risk of accidents, particularly when combined with heat or other environmental stresses (e.g., hypoxia).
- Better understanding of the relationship between body water deficits and heat stroke or cardiac arrest associated with intense physical activity.
- The influence of hydration status on morbidity-associated fever and infection outcome.
- The effects of hydration status and fluid intake on the occurrence of urinary tract infections.

- The effects of hydration status and fluid intake on chronic diseases, such as kidney stones and cholelithiasis, as well as the occurrence of specific cancers, including colon cancer and bladder cancer.
- The effects of chronic overhydration, in the presence of adequate sodium intake, on health and cognitive ability.
- The mechanistic effects by which dehydration can contribute to exertional heat injury and stroke.

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5
Potassium

SUMMARY

Potassium, the major intracellular cation in the body, is required for normal cellular function. Severe potassium deficiency is characterized by hypokalemia—a serum potassium concentration of less than 3.5 mmol/L. The adverse consequences of hypokalemia include cardiac arrhythmias, muscle weakness, and glucose intolerance. Moderate potassium deficiency, which typically occurs without hypokalemia, is characterized by increased blood pressure, increased salt sensitivity,[1] an increased risk of kidney stones, and increased bone turnover (as indicated by greater urinary calcium excretion and biochemical evidence of reduced bone formation and increased bone resorption). An inadequate intake of dietary potassium may also increase the risk of cardiovascular disease, particularly stroke.

The adverse effects of inadequate potassium intake can result from a deficiency of potassium *per se*, a deficiency of its conjugate anion, or both. In unprocessed foods, the conjugate anions of potassium are mainly organic anions, such as citrate, that are converted in the body to bicarbonate. Hence an inadequate intake of potassium is also associated with reduced intake of bicarbonate precursors. Acting as a buffer, bicarbonate neutralizes diet-derived noncarbonic

[1] In general terms, salt sensitivity is expressed as either the reduction in blood pressure in response to a lower salt intake or the rise in blood pressure in response to sodium loading.

acids, such as sulfuric acid generated from sulfur-containing amino acids commonly found in meats and other high protein foods. In the setting of an inadequate intake of bicarbonate precursors, buffers in the bone matrix neutralize the excess diet-derived acid, and in the process, bone becomes demineralized. Excess diet-derived acid titrates bone and leads to increased urinary calcium and reduced urinary citrate excretion. The resultant adverse clinical consequences are possibly increased bone demineralization and increased risk of calcium-containing kidney stones. In processed foods to which potassium has been added and in supplements, the conjugate anion is typically chloride, which does not act as a buffer. Because the demonstrated effects of potassium often depend on the accompanying anion and because it is difficult to separate the effects of potassium from the effects of its accompanying anion, this report primarily focuses on research pertaining to nonchloride forms of potassium—the forms found naturally in fruits, vegetables, and other potassium-rich foods.

On the basis of available data, an Adequate Intake (AI) for potassium is set at 4.7 g (120 mmol)/day for all adults. This level of dietary intake (i.e., from foods) should maintain lower blood pressure levels, reduce the adverse effects of sodium chloride intake on blood pressure, reduce the risk of recurrent kidney stones, and possibly decrease bone loss. Because of insufficient data from dose-response trials demonstrating these effects, an Estimated Average Requirement (EAR) could not be established, and thus a Recommended Dietary Allowance (RDA) could not be derived.

At present, dietary intake of potassium by all groups in the United States and Canada is considerably lower than the AI. In recent surveys, the median intake of potassium by adults in the United States was approximately 2.8 to 3.3 g (72 to 84 mmol)/day[2] for men and 2.2 to 2.4 g (56 to 61 mmol)/day for women; in Canada, the median intakes ranged from 3.2 to 3.4 g (82 to 87 mmol)/day for men and 2.4 to 2.6 g (62 to 67 mmol)/day for women (Appendix Tables D-5 and F-3). Because African Americans have a relatively low intake of potassium and a high prevalence of elevated blood pressure and salt sensitivity, this subgroup of the population would especially benefit from an increased intake of potassium.

In the generally healthy population with normal kidney function, a potassium intake from foods above the AI poses no potential for

[2] To convert millimoles (mmol) of potassium to milligrams (mg) of potassium, multiply mmol by 39.1 (the molecular weight of potassium).

increased risk because excess potassium is readily excreted in the urine. Therefore, a Tolerable Upper Intake Level (UL) was not set. However, in individuals in whom urinary excretion of potassium is impaired, a potassium intake below 4.7 g (120 mmol)/day is appropriate because of adverse cardiac effects (arrhythmias) from the resulting hyperkalemia (a markedly elevated serum potassium concentration). Such individuals are typically under medical supervision.

Common drugs that can substantially impair potassium excretion are angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and potassium-sparing diuretics. Medical conditions associated with impaired urinary potassium excretion include diabetes, chronic renal insufficiency, end-stage renal disease, severe heart failure, and adrenal insufficiency. Elderly individuals are at increased risk of hyperkalemia because they often have one or more of these conditions or are treated with one of these medications.

BACKGROUND INFORMATION

Function

The major intracellular cation in the body is potassium, which is maintained at a concentration of about 145 mmol/L of intracellular fluid, but at much lower concentrations in the plasma and interstitial fluid (3.8 to 5 mmol/L of extracellular fluid). Relatively small changes in the concentration of extracellular potassium greatly affect the extracellular:intracellular potassium ratio and thereby affect neural transmission, muscle contraction, and vascular tone.

Physiology of Absorption and Metabolism

In unprocessed foods, potassium occurs mainly in association with bicarbonate-generating precursors like citrate, and to a lesser extent with phosphate. In foods to which potassium is added in processing and in supplements, the form of potassium is potassium chloride. In healthy persons, approximately 85 percent of dietary potassium is absorbed (Holbrook et al., 1984). The high intracellular concentration of potassium is maintained via the activity of the Na^+/K^+-ATPase pump. Because this enzyme is stimulated by insulin, alterations in the plasma concentration of insulin can affect cellular influx of potassium and thus plasma concentration of potassium.

The preponderance of dietary potassium (approximately 77 to 90 percent) is excreted in urine, while the remainder is excreted mainly in feces, with much smaller amounts being lost in sweat (Agarwal et al., 1994; Holbrook et al., 1984; Pietinen, 1982). The correlation between dietary potassium intake and urinary potassium content is high ($r = 0.82$) (Holbrook et al., 1984). The great majority of potassium that is filtered by the glomerulus of the kidney is reabsorbed (70 to 80 percent) in the proximal tubule such that only a small amount of filtered potassium reaches the distal tubule. The majority of potassium in urine results from secretion of potassium into the cortical collecting duct, a secretion regulated by a number of factors, including the hormone aldosterone. An elevated plasma concentration of potassium stimulates the adrenal cortex to release aldosterone, which in turn increases secretion of potassium in the cortical collecting duct and hence into urine.

Potassium and Acid-Base Considerations

A diet rich in potassium from fruits and vegetables favorably affects acid-base metabolism because these foods are rich in precursors of bicarbonate, which neutralizes diet-induced acid *in vivo* (Sebastian et al., 1994, 2002). The net quantitative outcome of this acid-base interaction is termed "the net endogenous acid production" (NEAP). Because most endogenous noncarbonic acid is derived from protein, and because most endogenous bicarbonate (base) is derived from organic anions present in potassium-rich fruits and vegetables, the dietary protein-to-potassium ratio closely estimates NEAP and thus predicts urinary net acid excretion, which in turn predicts calcium excretion. For many years it has been hypothesized that the modern Western diet could induce a low-grade metabolic acidosis that in turn could induce bone demineralization, osteoporosis, and kidney stones (Barzel, 1995; Barzel and Jowsey, 1969; Lemann et al., 1966; Wachman and Bernstein, 1968). The results of several recent epidemiological (New et al., 1997, 2000; Tucker et al., 1999) and metabolic (Maurer et al., 2003; Morris RC et al., 2001; Sebastian et al., 1994) studies support this hypothesis.

Noncarbonic acids are generated from metabolism of both plant and animal proteins (e.g., in both, sulfuric acid is generated from the metabolism of sulfur-containing amino acids found in meats, fish, dairy products, grains, and to a lesser extent, in fruits and vegetables). Unlike fruits and vegetables, meats and other animal foods contain few precursors of bicarbonate. The only plant food group that consistently yields noncarbonic acid precursors in excess

of bicarbonate precursors is cereal grains (e.g., wheat, rice, and barley). Thus the typical Western diet is usually a net producer of noncarbonic acids not only because of its large content of acid-generating animal proteins, but also because of large amounts of cereal grain products and relatively lower amounts of bicarbonate-generating plant foods (Kurtz et al., 1983; Lemann et al., 1966; Lennon et al., 1966; Sebastian et al., 2002). Although the premodern diet contained considerable amounts of meat (Sebastian et al., 2002), it was a net producer of bicarbonate because it also contained large amounts of fruits and vegetables that generated substantial amounts of bicarbonate via metabolism (Eaton et al., 1999; Sebastian et al., 2002). Accordingly, humans evolved to excrete large loads of bicarbonate and potassium, not the large net acid loads chronically generated by the current Western dietary patterns.

The renal acidification process in humans does not completely excrete the modern acid load (Frassetto et al., 1996; Kurtz et al., 1983; Lennon et al., 1966; Sebastian et al., 1994). The unexcreted acid does not titrate plasma bicarbonate to ever lower concentrations, but rather to sustained concentrations only slightly lower than those that otherwise occur. This is because the unexcreted hydrogen ion not only exchanges with bone sodium and potassium, but also titrates and is neutralized by basic salts of bone (Bushinsky, 1998; Lemann et al., 1966, 2003). Although preventing the occurrence of frank metabolic acidosis, the acid titration of calcium-containing carbonates and hydroxyapatite mobilizes bone calcium and over time dissolves bone matrix (Barzel, 1995; Bushinsky, 1998; Bushinsky and Frick, 2000; Lemann et al., 1966, 2003). The buffering by bone of diet-derived acid may be regarded as a biological tradeoff (Alpern, 1995; Morris RC et al., 2001). At the cost of bone demineralization, arterial pH and plasma bicarbonate concentration are only modestly reduced by an acidogenic diet, such as the Western-type diet (Morris RC et al., 2001), and not to values below their "normal" range. These normal reduced values, however, reflect a state of low-grade metabolic acidosis.

INDICATORS CONSIDERED FOR ESTIMATING THE REQUIREMENT FOR POTASSIUM

This section reviews potential physiological indices and pathologic endpoints for adverse effects of insufficient dietary intake of potassium in apparently healthy individuals. Because the demonstrated effects of potassium often depend on the accompanying anion and

because it is difficult to separate the effects of potassium from the effects of its accompanying anion, this report focuses primarily on research pertaining to nonchloride forms of potassium—the forms found naturally in foods.

Potassium Balance

As previously mentioned, urinary potassium excretion reflects dietary potassium intake. The effects on potassium balance of two levels of potassium intake (3.1 g [80 mmol]/day and 11.7 g [300 mmol]/day) were examined in six healthy men about 24 years of age (Hene et al., 1986). After 18 days on the high potassium diet, urinary potassium excretion increased from 2.0 to 9.1 g (50 to 233 mmol)/day. In a separate study, daily fecal potassium loss ranged from 0.11 to 0.85 g (2.8 to 22 mmol)/day on dietary intakes approximating 2.6 to 2.9 g (66 to 74 mmol)/day (Holbrook et al., 1984). Losses of potassium in sweat vary; under conditions in which sweat volume is minimal, the reported values range from 2.3 to 16 mmol (90 to 626 mg)/L (Consolazio et al., 1963).

A number of dietary factors, including dietary fiber and sodium, can affect potassium balance. The effects of increased wheat fiber intake on fecal potassium loss were examined in six healthy men, 21 to 25 years of age, who consumed 45 g/day of wheat fiber for 3 weeks; their previous average intake was 17 g/day. Potassium intake was held constant at 3.1 g (80 mmol)/day (Cummings et al., 1976). Fecal weight increased significantly from about 79 g/day to about 228 g/day with the increased fiber intake. Fecal potassium loss also significantly increased from a prestudy level of 0.3 g to a final value of 1.1 g (8.6 to 28.5 mmol)/day (Cummings et al., 1976).

The level of sodium intake does not appear to influence potassium excretion (Bruun et al., 1990; Castenmiller et al., 1985; Overlack et al., 1993; Sharma et al., 1990; Sullivan et al., 1980) except at levels of sodium intake above 6.9 g (300 mmol)/day, at which point net loss of potassium has been demonstrated (Kirkendall et al., 1976; Luft et al., 1982). At dietary sodium intakes greater than 6.9 g (300 mmol)/day, there was a net loss of potassium—urinary potassium excretion exceeded dietary intake, at least during the 3-day periods in this trial (Luft et al., 1982). Over the long term, net potassium losses do not occur at lower levels of sodium intake. At three levels of dietary sodium, 1.5, 2.4, and 3.2 g (65, 104, and 140 mmol)/day, each provided for 28 days, urinary potassium excretion did not exceed intake and urinary potassium excretion was similar at each sodium level (Sacks et al., 2001).

In nonhypertensive individuals who maintained potassium balance while consuming at least 1.6 g (40 mmol)/day of potassium, serum potassium concentrations were at the lower end of the clinically accepted normal range (Sebastian et al., 1971). As discussed subsequently, while potassium balance can be maintained at this lower level of dietary intake, if such levels are consumed chronically, clinically important adverse effects may result (Morris RC et al., 2001).

Serum Potassium Concentration

Serum potassium concentration, as well as body potassium content, is determined jointly by the amount of potassium consumed and the amount excreted since the gastrointestinal tract normally absorbs 85 percent of dietary intake and because the kidney excretes most of the potassium absorbed (Young, 1985, 2001; Young and McCabe, 2000).

Humans evolved from ancestors who habitually consumed large amounts of uncultivated plant foods that provided substantial amounts of potassium. In this setting, the human kidney developed a highly efficient capacity to excrete excess potassium. The normal human kidney efficiently excretes potassium when dietary intake is high enough to increase serum concentration even slightly, but inefficiently conserves potassium when dietary intake and thus serum concentration is reduced (Young, 2001). While normal renal function protects against the occurrence of hyperkalemia when dietary potassium is increased, it does not prevent the occurrence of potassium deficiency when dietary intake of potassium is reduced (Squires and Huth, 1959), even marginally, relative to the usual potassium intake in the Western diet. Based on recent diet surveys, the estimated median potassium intakes for adult age groups in the United States (Appendix Table D-5) ranged from 2.8 to 3.3 g (72 to 84 mmol)/day for men and 2.2 to 2.4 g (56 to 61 mmol)/day for women, while median intakes in Canada from surveys conducted between 1990 and 1999 ranged from 3.2 to 3.4 g (82 to 87 mmol)/day for men and 2.4 to 2.6 g (62 to 67 mmol)/day for women (Appendix Table F-2).

Signs and symptoms of potassium deficiency can occur without frank hypokalemia (i.e., they occur while the serum potassium concentration remains at or somewhat above 3.5 mmol/L, an accepted minimum of the range for normal serum potassium levels) (Table 5-1). In generally healthy people, frank hypokalemia is not a necessary or usual expression of a subtle dietary potassium deficiency. As

TABLE 5-1 Dietary Potassium and Serum Potassium Concentrations

Reference	Subjects	Dietary Potassium (K),[a] g/d (mmol/d)	Serum Potassium (mmol/L) ± standard deviation
Dluhy et al., 1972	8 women, 2 men, crossover	1.6 (40)	4.1 ± 0.1[b]
	5 subjects, 6–7 d, 0.23 g (10 mmol) sodium (Na)/d	7.8 (200)	4.3 ± 0.1[b]
		1.6 (40)	4.0 ± 0.1[b]
	5 subjects, 3 d, 4.6 g (200 mmol) Na/d	7.8 (200)	4.2 ± 0.1[b]
Zoccali et al., 1985	5-d crossover, 10 men	3.0 (76)	3.9 ± 0.1[b]
		6.9 (176)	4.3 ± 0.1[b]
Hene et al., 1986	18-d parallel, 6 men	3.1 (80)	4.26 ± 0.28[b]
		11.7 (300)	4.39 ± 0.32[b]
Witzgall and Behr, 1986	6 d on high K diet, 16 men	2.3 g (60)	4.2 ± 0.3[b]
		10.1 g (260)	4.6 ± 0.3[c]
Grimm et al., 1990	2.2 yr supplement/placebo intervention, 287 men, 45–68 yr, baseline urinary K = 2.2 g/d	+ 3.8 (96)	4.2[b]
		+ 0	4.5[c]
			The difference averaged 0.26 mmol/L over the 2-yr period
Rabelink et al., 1990	20 d, 6 men	3.9 (100)	3.75 ± 0.16[b]
		15.6 (400)	4.22 ± 0.12[b]
Clinkingbeard et al., 1991	3-d crossover, 8 men	0.39 (10)	3.8 ± 0.1[b]
		7.8 (200)	4.3 ± 0.2[c]
Deriaz et al., 1991	5-d crossover, 8 men	2.7 (69)	4.1 ± 0.2[b]
		6.4 (163)	3.8 ± 0.1[c]
Valdes et al., 1991	4-wk crossover, 24 men and women, provided placebo or supplement	+ 0	3.8 ± 0.1[b]
		+ 2.5 (64)	4.1 ± 0.1[c]
Smith et al., 1992	4-d crossover, 22 men and women	2.7 (70)	3.9 ± 0.1[b]
		4.7 (120)	4.3 ± 0.1[c]
Sebastian et al., 1994	18 d, 18 postmenopausal women	2.3 (60)	3.9 ± 0.15[b]
		+ 4.7 (120)	4.0 ± 0.2[b]
Morris et al., 1999b	38 men, parallel	+ 1.17 (30)	3.7 ± 0.2[b]
		4.7 (120)	4.0 ± 0.2[c]
Coruzzi et al., 2001	10-d isocaloric crossover, 8 men, 3 women	0.70 (18)	3.2 ± 0.1 (standard error)[b]
		3.1 (80)	4.1 ± 0.05[c]

[a] "+" means amount of potassium provided as a supplement.
[b,c] Values with different superscripts differed significantly at $p < 0.05$ or less.

will be discussed in subsequent sections, a typical dietary intake of potassium that gives rise to a serum potassium concentration somewhat greater than 3.5 mmol/L would still be considered inadequate if a higher intake of potassium prevents, reduces, or delays expression of certain chronic diseases or conditions, such as elevated blood pressure, salt sensitivity, kidney stones, bone loss, or stroke (Morris et al., 1999a, 1999b; Morris RC et al., 2001; Schmidlin et al., 1999; Sudhir et al., 1997).

The Western diet gives rise not only to low-grade potassium deficiency, but also to low-grade bicarbonate deficiency that is expressed as low-grade metabolic acidosis (Morris et al., 1999a, 1999b; Morris RC et al., 2001; Sebastian et al., 2002). Because plasma concentrations of potassium and other electrolytes (bicarbonate, sodium, and chloride) are highly regulated, their plasma concentrations remain normal or little changed despite substantial increases in dietary potassium intake (Lemann et al., 1989, 1991; Morris RC et al., 2001; Schmidlin et al., 1999). Thus serum potassium is not a sensitive indicator of potassium adequacy related to mitigating chronic disease.

Hypokalemia

Disordered potassium metabolism that is expressed as hypokalemia (that is, a serum potassium level below 3.5 mmol/L) can result in cardiac arrhythmias, muscle weakness, hypercalciuria, and glucose intolerance. Such disorders, which are correctable by potassium administration, can be induced by diuretics, chloride-depletion associated forms of metabolic alkalosis, and increased aldosterone production (Knochel, 1984).

Hypokalemia reduces the capacity of the pancreas to secrete insulin and therefore is a recognized reversible cause of glucose intolerance (Helderman et al., 1983). There is some limited evidence that hypokalemia can also confer insulin resistance (Helderman et al., 1983; Pollare et al., 1989). A low potassium diet (0.58 g [15 mmol]/day), which did not induce frank hypokalemia, resulted in a decrease in plasma insulin concentration and a resistance to insulin action, which were reversed when dietary potassium was supplemented with 4.8 g (64 mmol)/day of potassium chloride (Norbiato et al., 1984). Decreased erythrocyte and plasma potassium concentrations have been associated with glucose intolerance (Modan et al., 1987). Diuretic-induced hypokalemia leads to insulin resistance (hyperglycemia and hyperinsulinemia) and glucose intolerance (Helderman et al., 1983; Plavinik et al., 1992). In one trial, individu-

als with diuretic-induced hypokalemia did not achieve reduction in cardiovascular events compared with diuretic-treated individuals without hypokalemia (Franse et al., 2000).

Because moderate potassium deficiency and its adverse side effects occur without hypokalemia, hypokalemia is not a sensitive indicator appropriate for use to establish adequacy.

Salt-Sensitive Blood Pressure

The extent to which blood pressure responds to changes in sodium chloride intake varies among individuals. "Salt-sensitive" blood pressure is that which varies directly with the intake of sodium chloride (Morris et al., 1999b; Weinberger, 1996). Salt sensitivity, even in those who are nonhypertensive, has been found to confer its own cardiovascular risks, including incident hypertension and cardiovascular death (Morimoto et al., 1997; Weinberger et al., 2001). Salt sensitivity occurs with greater frequency and severity in nonhypertensive African Americans than in nonhypertensive whites (Morris et al., 1999b; Price et al., 2002; Weinberger, 1996).

The expression of salt sensitivity is strongly modulated by dietary potassium intake (Morris et al., 1999b; Schmidlin et al., 1999; Luft et al., 1979). In a metabolic study of 38 healthy, nonhypertensive men (24 African Americans and 14 whites) fed a basal diet with low levels of potassium (1.2 g [30 mmol]/day) and sodium (0.7 g [30 mmol]/day), the modulating effect of potassium supplementation on the pressor effect of dietary sodium chloride loading (14.6 g [250 mmol]/day) was investigated (Morris et al., 1999b) (Figure 5-1). Before potassium was supplemented, 79 percent of the African-American men and 26 percent of the white men were termed salt sensitive, as defined by a sodium chloride-induced increase in mean arterial pressure of at least 3 mm Hg. Salt sensitivity was defined as "severe" if sodium chloride induced an increase in mean arterial pressure of 10 mm Hg or more, an increase observed only in African-American men. When dietary potassium was increased with potassium bicarbonate from 1.2 g (30 mmol)/day to 2.7 g (70 mmol)/day, over half of the African-American men, but only one-fifth of the white men, remained salt sensitive. In the African Americans with severe salt sensitivity, increasing dietary potassium to a high-normal intake of 4.7 g (120 mmol)/day reduced the frequency of salt sensitivity to 20 percent, the same percentage as that observed in white subjects when their potassium intake was increased to only 2.7 g (70 mmol)/day. In another metabolic study of 16 mostly nonhypertensive African-American subjects loaded with 14.6 g (250 mmol) of

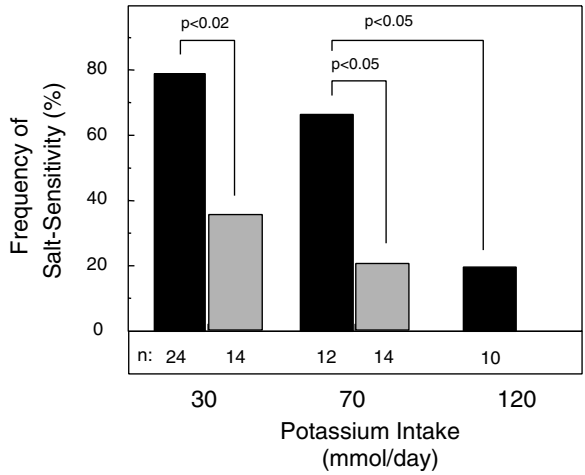

FIGURE 5-1 Effect of potassium intake on frequency of salt sensitivity in nonhypertensive African-American men (solid bar) and white men (gray bar). No white men were tested with 4.7 g (120 mmol)/day of potassium. Throughout an initial 7-day period of salt loading in all study subjects, potassium intake as potassium bicarbonate was set at 1.2 g (30 mmol)/day, then increased to a total of either 2.7 or 4.7 g (70 or 120 mmol)/day for a subsequent 7-day period of salt loading. Reprinted with permission from Morris et al. (1999b). Copyright 1999 by W.B. Saunders Co.

sodium chloride per day, increasing dietary potassium as potassium bicarbonate to an intake of 6.6 g (170 mmol)/day abolished the salt sensitivity of all subjects (Schmidlin et al., 1999).

In aggregate, these trials document that supplemental potassium bicarbonate mitigates the pressor effect of dietary sodium chloride in a dose-dependent fashion. Furthermore, these trials highlight the potential benefit of increased potassium intake in African Americans, who have a higher prevalence of hypertension and of salt sensitivity and a lower intake of potassium than non-African Americans. Survey data from the Third National Health and Nutrition Examination Survey (NHANES III) in the United States (Appendix Tables D-6 and D-7) estimated that the median intake of potassium of non-Hispanic African-American men (aged 19 to 30 years) was 3.0 g (78 mmol)/day, while that for non-Hispanic white men (aged 19 to 30 years) was 3.4 g (87 mmol)/day, approximately 10 percent lower than their white counterparts. Similar differences

are noted for women, with non-Hispanic white women aged 19 to 30 years having higher intakes than non-Hispanic African-American women of the same age group.

Predictably, over the range of dietary potassium evaluated in the study of salt sensitivity (Figure 5-1), the serum concentration of potassium remained well within the normal range, increasing only minimally (from ≈ 3.8 to 4.0 mmol/L) when potassium bicarbonate was supplemented (Morris et al., 1999b). It has been postulated that such dose-dependent suppression of salt sensitivity might prevent or delay the occurrence of hypertension (Berenson et al., 1979; Frisancho et al., 1984; Grim et al., 1980; Morris et al., 1999b). In hypertensive individuals, potassium supplementation can mitigate the pressor effect of sodium chloride (Iimura et al., 1981; Morgan et al., 1984).

The antipressor effect of dietary potassium may in part result from its natriuretic effects (Morris et al., 1999b; Schmidlin et al., 1999). As mentioned earlier, potassium acts directly on the renal tubule to increase the urinary excretion of sodium chloride (Brandis et al., 1972; Stokes et al., 1982), an action apparently unaffected by the anion accompanying ingested potassium (van Buren et al., 1992).

Blood Pressure

Epidemiological Evidence

Numerous observational studies (Table 5-2) have examined the relationship between blood pressure and dietary potassium intakes, or urinary potassium excretion, used as a proxy of intake (Ascherio et al., 1992; Dai et al., 1984; Dyer et al., 1994; Geleijnse et al., 1996; Hajjar et al., 2001; Khaw and Barrett-Connor, 1984; Langford, 1983; Liu et al., 1988, 1996; Rose et al., 1988; Takemori et al., 1989; Tunstall-Pedoe, 1999; Walker et al., 1979). Many, but not all, studies documented an inverse association—that is, a higher intake of potassium that was associated with lower blood pressure. In the Intersalt study, a 50-mmol (2.0-g) higher excretion of urinary potassium was associated with a 2.5- and 1.5-mm Hg lower level of systolic and diastolic blood pressure, respectively (Rose et al., 1988).

While blood pressure is inversely associated with potassium intake and directly associated with sodium intake and the sodium:potassium ratio, blood pressure is typically more closely associated with the sodium:potassium ratio than intake of either electrolyte alone. This pattern was evident in Intersalt and in other observational studies (Khaw and Barrett-Connor, 1988; Morris and Sebastian, 1995;

TABLE 5-2 Epidemiological Studies on Potassium Intake and Blood Pressure

Reference	Study Design
Walker et al., 1979	Cross-sectional, 574 men and women
Khaw and Barrett-Connor, 1984	Cross-sectional, 685 men and women
Kok et al., 1986	Cross-sectional, 2,291 men and women in the Netherlands, multivariate analysis
Kesteloot and Joossens, 1988	Belgian Interuniversity Research on Nutrition and Health Study, cross-sectional, 8,058 men and women
Khaw and Barrett-Connor, 1988	Cross-sectional, 1,302 men and women
Liu et al., 1988	Cross-sectional, 3,248 men and women in China
Rose et. al., 1988	Intersalt study, cross-sectional, 10,648 men and women
Takemori et al., 1989	Cross-sectional, 7,441 women in Japan
Witteman et al., 1989	Nurses Health Study, prospective, 4-yr follow up, 58,218 women, multivariate analysis
Khaw and Barrett-Connor, 1990	Cross-sectional, 2,046 men and women
Ascherio et al., 1992	Health Professionals Follow-Up Study, prospective 4-yr follow-up, 30,681 men, multivariate analysis

Results[a]
Urinary K was inversely correlated with DBP
Dietary K intake inversely correlated with age-adjusted SBP in men and women and age-adjusted DBP in men
No significant association between blood pressure and potassium intake
No independent effects of dietary K intake on BP
Blood pressure varied directly with dietary Na:K ratio, age-adjusted SBP and DBP significantly and inversely correlated with potassium intake
Urinary potassium was inversely correlated with DBP and SBP only in the 20- to 29-yr-old age group
Urinary K was inversely correlated with blood pressure
Urinary potassium inversely correlated with blood pressure
Potassium intake g/d (mmol/d) RR of hypertension Q1 < 2.0 (51) 1.0 Q2 2.0–2.39 (51–61) 0.93 Q3 2.4–2.79 (61–71) 1.02 Q4 2.8–3.19 (72–82) 1.05 Q5 > 3.2 (82) 1.05 $p = 0.26$ No independent association with potassium intake and risk of hypertension
Age-adjusted SBP and DBP correlated significantly and directly with Na:K ratio
Potassium intake g/d (mmol/d) RR of hypertension Q1 < 2.4 (61) 1.2 Q2 2.4–2.79 (61–71) 1.1 Q3 2.8–3.19 (72–82) 1.0 Q4 3.2–3.59 (82–92) 1.1 Q5 > 3.6 (92) 1.0 $p = 0.41$ No independent association with potassium intake and risk of hypertension

continued

TABLE 5-2 Continued

Reference	Study Design
Dyer et al., 1994	Intersalt study, cross-sectional, 10,079 men and women
Zhou et al., 1994	Cross-sectional, 705 men and women in China
Geleijnse et al., 1996	Rotterdam Study, cross-sectional, 3,239 men and women
Liu et al., 1996	CARDIA Study, cross-sectional, 4,146 men and women
Tunstall-Pedoe, 1999	Scottish Heart Health Study, cross-sectional, 11,629 men and women
Hajjar et al., 2001	NHANES III, cross-sectional, 17,030 men and women, multivariate analysis

[a] DBP = diastolic blood pressure, SBP = systolic blood pressure, K = potassium, Na = sodium, BP = blood pressure, RR = relative risk, Q = quintile of potassium intake.

Zhou et al., 1994). Still, because of high colinearity of nutrient intake (Rose et al., 1988), it is difficult to tease apart the effects of potassium from the effects of other nutrients closely associated with potassium in foods.

Evidence from Intervention Studies

Results from intervention studies demonstrate that potassium can reduce blood pressure in nonhypertensive (Tables 5-3 and 5-4) as well as hypertensive individuals (Tables 5-3 and 5-5). Table 5-3 provides corresponding results for studies in which potassium was increased through diet, while Tables 5-4 and 5-5 provide corresponding results for studies in which potassium was increased by use of potassium supplements. Although the trials in Tables 5-4 and 5-5 tested the effect of supplemental potassium, their findings are assumed to apply to potassium from foods as well. A few studies have tested the effects of diets rich in potassium (Appel et al., 1997; Sacks et al., 2001). One other trial documented that increased fruit and vegetable intake can reduce blood pressure, but it did not

Results[a]
A 0.6 g (15 mmol) increase in potassium intake was associated with an estimated mean change in SBP of –1.0 mm Hg
A positive association with SBP and sodium:potassium ratio in the setting of low calcium intakes
An increase in K intake of 1 g/d (26 mmol/d) was associated with a 0.9 mm Hg lower SBP and 0.8 mm Hg lower DBP
Potassium intake was significantly and inversely related to blood pressure in white women and African-American men
Potassium excretion was significantly and inversely associated with blood pressure, especially SBP in men
SBP and DBP were inversely associated with K intake

specify the amount of dietary potassium provided by the increased fruit and vegetable diet (John et al., 2002). Because of the potential for confounding from concomitant changes in other nutrients (e.g., fiber and magnesium), evidence from Table 5-3 should be interpreted with caution.

A number of the supplemental studies gave potassium supplements (e.g., potassium chloride) without documenting the amount of potassium in the diet (Tables 5-4 and 5-5). Hence, total intake of potassium from diet and supplements in some of the studies is unknown. It should also be recognized that none of the studies listed in Tables 5-3, 5-4, or 5-5 provide more than two levels of potassium; thus a dose-response assessment within the same study is unavailable.

In the absence of large-scale trials, pooling of the results of small clinical trials provides a more statistically precise estimate of intervention effects and allows for the exploration of the basis for heterogeneity in outcome effects. At least three major meta-analyses of the effects of oral potassium in the treatment and prevention of human hypertension have been conducted (Cappuccio and MacGregor, 1991; Geleijnse et al., 2003; Whelton et al., 1997). The meta-

TABLE 5-3 Intervention Studies Evaluating the Effect of Changes in Dietary Potassium Intake from Foods on Blood Pressure

Reference	Study Design	Potassium Intake, g/d (mmol/d) by Group
Nonhypertensive individuals		
Lawton et al., 1990[b]	6-d crossover, 10 men; formula diet + foods	1.2 (29) 3.9 (92)
Appel et al., 1997[d,e]	8-wk parallel, 326 men and women	1.8 (45) = control diet 4.1 (105) = fruit/veg 4.4 (113) = DASH
Hypertensive individuals		
Lawton et al., 1990	6-d crossover, 11 men; formula diet + foods	1.2 (29) 3.9 (92)
Appel et al., 1997[d,e]	8-wk parallel, 133 men and women	1.8 (45) = control diet 4.1 (105) = fruit/veg 4.4 (113) = DASH

[a] At end of dietary period.
[b] As determined by random analysis of sample diets.
[c] Difference in response to diet intervention pre- and post- between control and experimental group; SBP = systolic blood pressure, DBP = diastolic blood pressure.

analysis by Whelton and colleagues (1997) and the one by Geleijnse and coworkers (2003) were confined to randomized controlled trials in which the only difference between the intervention and control groups was potassium intake. Both assessed the potential input of confounders, while the analysis by Whelton presented data from individual trials, including estimates of potassium intake.

Of the 33 trials included in the meta-analysis by Whelton and coworkers (1997) (see studies marked in Tables 5-3 and 5-5), there were 2,609 African-American and white participants (18 to 79 years of age). Twelve trials were conducted in nonhypertensive individu-

Sodium Intake, g/d (mmol/d)	Urinary Potassium,[a] mmol/d, During Follow-up	Urinary Sodium,[a] mmol/d, During Follow-up	Blood Pressure (mm Hg) Changes		Statistical Significance
			$n = 7$		Δ SBP significant at $p < 0.01$
8.5 (371)	27	302	123/69		
8.5 (368)	62	343	116/72		
			SBP[c]	DBP[c]	
3.0 (132)	39	138	—	—	
2.8 (122)	71	130	↓ 0.8	↓ 0.3	
2.9 (124)	75	134	↓ 3.5	↓ 2.1	
		$n = 8$			Δ SBP significant at $p < 0.001$
8.5 (371)	30	322	134/79		
8.5 (368)	76	324	124/76		
			SBP[c]	DBP[c]	
3.0 (132)	39	138	—	—	
2.8 (122)	71	130	↓ 7.2	↓ 2.8	
2.9 (124)	75	134	↓ 11.4	↓ 5.5	

[d] Estimate of nutrient intake based on chemical analysis of 2,100 kcal menu; three food-based diets: control diet, fruit/veg diet (higher in fruits and vegetables), and DASH diet (higher in fruits, vegetables, and dairy, lower in meats, fats, and sweets).

[e] Urinary excretion averaged over both nonhypertensive and hypertensive subjects.

NOTE: Difference in response to diet intervention significant at $p \leq 0.01$.

als (1,005 participants) and 21 trials were conducted in individuals with hypertension (1,560 participants). Hypertensive patients received antihypertensive medications concurrently in 4 of the 21 trials. All but six of the trials provided potassium in the form of potassium chloride. As such, there was little capacity to compare the efficacy of different potassium salts. Just one trial tested potassium citrate as well as potassium chloride (Mullen and O'Conner, 1990). In this small, placebo-controlled trial, neither form of potassium significantly affected blood pressure.

Average net change in urinary potassium excretion for the inter-

TABLE 5-4 Clinical Trials on the Effects of Potassium Supplements on Blood Pressure in Nonhypertensive Individuals in Order of Increasing Duration of Intervention

Reference	Subjects	Study Design	Potassium Intake,[b] g/d (mmol/d)
Barden et al., 1991[a]	37 women	4-d crossover	Placebo 3.1 (80) KCl supplement
Gallen et al., 1998	10 men, 11 women	9-d crossover; K restriction; 4.1 g (180 mmol) Na	0.78 (20) diet plus placebo 3.1 (80) KCl supplement
Krishna et al., 1989[a]	10 men	10-d crossover; 2.8–4.6 (120–200 mmol) Na	0.4 (10) diet plus placebo 3.5 (90) [80 KCl supplement]
Skrabal et al., 1981[a]	20 men	2-wk crossover	3.1 (80) KCl supplement [4.6 (200) Na] 3.1 (80) KCl supplement [1.2 (50) Na] 7.8 (200) KCl supplement [4.6 (200) Na] 7.8 (200) KCl supplement [1.2 (50) Na]
Khaw and Thom, 1982[a]	20 men	2-wk crossover	1.6 (41) diet 2.5 (64) KCl supplement
Poulter and Sever, 1986[a]	19 men	2-wk crossover	Placebo 2.5 (64) KCl supplement
Mullen and O'Connor, 1990[a]	24 men	2-wk crossover	Placebo 2.9 (75) KCl supplement 2.9 (75) K citrate supplement
Brancati et al., 1996[a]	31 men, 56 women	3-wk parallel, 2.9–4.0g (127–175 mmol) Na	Placebo plus 1.3-1.4 (32-35) K from diet 3.1 (80) KCl supplement plus 1.3-1.4 (32-35) K from diet

Urinary Electrolytes,[c] g/d (mmol/d) During Follow-up		Mean Blood Pressure (mm Hg) on Placebo or Control Diet[d]	Mean Net Change in Blood Pressure[e] (mm Hg)		
Potassium (K)	Sodium (Na)		SBP	DBP	Comments
2.1 (53)	2.4 (105)	105.9/64.1	—	—	
4.9 (125)	2.8 (120)		–1.7	–0.6	
2.5 (64)	3.2 (140)	MAP 82.7	MAP —		No significant difference between African-American and white participants
7.8 (20)	2.5 (109)		+3.7		
1.1 (28)	2.3 (100)	120.0/73.1	—	—	
2.9 (75)	3.3 (144)		–5.5	–7.4	
2.8 (71)	4.8 (210)	125.0/73.1	—	—	
2.5 (65)	0.9 (40)		–2.7	–3.0	
4.5 (116)	3.6 (155)		–1.7	–4.5	
6.7 (172)	0.6 (28)		–2.3	–3.5	
3.0 (78)	3.6 (155)	155.7/72.1	—	—	
5.1 (130)	3.8 (164)		–1.1	–2.4	
1.6 (41)	2.6 (113)	109.6/64.6	—	—	
3.1 (79)	2.6 (114)		–1.2	+2.0	
3.0 (77)	3.5 (153)	117/69	—	—	
3.9 (100)	3.2 (141)		0	+3.0	
4.3 (111)	3.2 (138)		–2.0	+2.0	
0.9 (25)	2.9 (130)	127/77	—	—	
3.5 (89)	3.3 (143)		–6.9	–2.5	

continued

TABLE 5-4 Continued

Reference	Subjects	Study Design	Potassium Intake,[b] g/d (mmol/d)
Barden et al., 1986[a]	44 women	4-wk crossover	Placebo 3.1 (80) KCl supplement
Naismith and Braschi, 2003	33 men, 26 women	6-wk parallel	Placebo plus 3.3 (84) diet 0.9 (24) KCl supplement plus 3.3 (84) diet
Whelton et al., 1995[a]	255 men, 98 women	24-wk parallel	Placebo 2.3 (60) KCl supplement
Hypertension Prevention Trial Research Group, 1990[a]	247 men, 144 women	3-yr parallel	3.9 (100) diet

[a] Included in meta analysis by Whelton et al. (1997).
[b] Potassium intake from diet unless otherwise indicated.
[c] Surrogate marker for electrolyte intake. CI = confidence interval.

vention versus the control (21 trials) in the meta-analysis (Whelton et al., 1997) varied from 0 to 129 mmol (5.0 g)/24 hours (median = 50 mmol [1.9 g]/24 hours) and was greater than or equal to 40 mmol (1.6 g)/24 hours in 21 (68 percent) trials. The weighted net change in urinary potassium was 53 mmol (2.1 g)/24 hours. Average net change in urinary sodium excretion for the intervention versus control ranged from –55 to +44 mmol (–1.3 g to +1.0 g)/24 hours, with a median of 7 mmol (0.3g)/24 hours. There was an intervention-related trend toward a reduction in systolic blood pressure in 26 of the 32 trials (81 percent), and in 11 trials (34 percent) the reduction in blood pressure was statistically significant. For diastolic blood pressure, an intervention-related trend toward reduction in blood pressure was noted in 24 of 33 trials (73 percent), and in 11 trials (30 percent) the reduction was statistically significant. Overall pooled estimates of the effects of potassium supplementation on systolic and diastolic blood pressure were –4.4 and –2.4 mm Hg, respectively ($p < 0.001$ for both values). Exclusion of an outlier

Urinary Electrolytes,[c] g/d (mmol/d) During Follow-up		Mean Blood Pressure (mm Hg) on Placebo or Control Diet[d]	Mean Net Change in Blood Pressure[e] (mm Hg)		
Potassium (K)	Sodium (Na)		SBP	DBP	Comments
1.9 (51)	2.9 (126)	118/71	—	—	
4.6 (118)	3.1 (136)		–1.4	–1.4	
	3.5 (151)	116/71	—	—	
	3.8 (166)		–7.6	–6.5	
2.1 (54)	3.3 (144)	121.6/81.1	—	—	
3.8 (97)	3.3 (144)		–0.13	–0.26	
2.5 (65)	3.5 (154)	124.1/82.3	–1.3	–0.9	

[d] MAP = mean arterial pressure.

[e] If potassium supplement, then change in blood pressure compared to placebo. SBP = systolic blood pressure, DBP = diastolic blood pressure.

trial (Obel, 1989) reduced the overall pooled effect size estimates to –3.1 mm Hg for systolic blood pressure and –2.0 mm Hg for diastolic blood pressure ($p < 0.001$ for both values) (Whelton et al., 1997).

When the analysis was restricted to the 29 trials with a documented intervention-related net change in urinary potassium greater than or equal to 20 mmol (0.8 g)/24 hours, the effect size estimates were –4.9 mm Hg for systolic and –2.7 mm Hg for diastolic blood pressure. These effect size estimates were also higher when analyses were restricted to the 29 trials in nonhypertensive and hypertensive individuals in whom no antihypertensive medications were administered (Whelton et al., 1997).

In subgroup analyses, there was a trend toward greater treatment-related reductions in systolic and diastolic blood pressure at higher levels of urinary sodium excretion during follow-up ($p < 0.001$). Linear regression analysis also identified a significant, independent positive relationship between average 24-hour urinary sodium ex-

TABLE 5-5 Clinical Trials on the Effects of Potassium Supplements on Blood Pressure in Hypertensive Individuals in Order of Increasing Duration of Intervention

Reference	Subjects	Study Design	Potassium Intake,[b] g/d (mmol/d)
Smith et al., 1992[a]	12 men 9 women	4-d crossover 4.6 g (200 mmol) Na	Placebo 4.7 (120) KCl
Krishna and Kapoor, 1991	10 men 2 women	10-d parallel; K restriction 2.8 g (120 mmol) Na	3.8 (96) [80 mmol KCl supplement] 0.62 (16) diet
Zoccali et al., 1985[a]	10 men 9 women	2-wk crossover	Placebo 3.9 (100) KCl supplement
MacGregor et al., 1982[a]	12 men 11 women	4-wk crossover	Placebo 2.5 (64) KCl supplement
Richards et al., 1984[a]	8 men 4 women	4- to 6-wk crossover; 4.1g (180 mmol) Na	2.3 (60) 7.8 (200)
Smith et al., 1985[a]	11 men 9 women	4-wk crossover; 1.6 g (70 mmol) Na	Placebo 2.5 (64) KCl supplement
Valdes et al., 1991[a]	13 men 11 women	4-wk crossover	Placebo 2.5 (64) KCl supplement
Fotherby and Potter, 1992[a]	5 men 13 women	4-wk crossover	Placebo 2.3 (60) KCl supplement
Kaplan et al., 1985[a]	6 men 10 women	6-wk crossover	Placebo 2.3 (60) KCl supplement
Matlou et al., 1986[a]	32 women	6-wk crossover	Placebo 2.5 (65) KCl supplement
Grobbee et al., 1987[a]	34 men 6 women	6-wk crossover	Placebo 2.8 (72) KCl supplement
Svetkey et al., 1987[a]	75 men 26 women	8-wk parallel	Placebo 4.7 (120) KCl supplement
Patki et al., 1990[a]	8 men 29 women	8-wk crossover	Placebo 2.3 (60) KCl supplement

Urinary Electrolytes,[c] g/d (mmol/d)		Mean Blood Pressure (mm Hg) Placebo or Control Diet	Mean Net Change in Blood Pressure[d] (mm Hg)		Comments
Potassium (K) g (mmol)	Sodium (Na) g (mmol)		SBP	DBP	
2.7 (70) 7.0 (179)	4.4 (192) 5.1 (221)	150.5/85.9	— –4.3	— –1.7	
1.1 (27)	1.9 (83)	141/96	—	—	Isocaloric diets
2.8 (72)	2.5 (110)		+7	+6	
2.3 (58) 5.4 (139)	4.2 (182) 4.5 (195)	147/92	–1.0	–3.0	Lying BP
2.4 (62) 4.6 (118)	3.2 (140) 3.9 (169)	155/99	— –7.0	— –4.0	
2.4 (61) 7.4 (190)	4.6 (200) 4.7 (205)	149.9/92.4	— –1.9	— –1.0	
2.6 (67) 4.6 (117)	1.7 (73) 1.8 (80)	162/103	— –2.0	— 0	
2.2 (55) 4.8 (123)	3.4 (147) 3.8 (166)	145/92	— –7.0	— –3.0	
2.3 (60) 3.9 (99)	2.8 (123) 3.1 (136)	186/100	— –10.0	— –6.0	
1.4 (36) 3.2 (82)	3.9 (168) 3.9 (169)	133.2/97.7	— –5.6	— –5.8	Subjects treated with antihypertensive medication
2.0 (52) 4.5 (114)	2.9 (130) 3.8 (165)	151/103	— –7.0	— –3.0	
2.9 (74) 5.1 (131)	1.3 (57) 1.6 (69)	135.7/72.5	— –2.5	— –0.6	
Not given	Not given	142/92.4	— –0.9	— –1.3	
2.3 (60) 3.2 (82)	4.6 (198) 4.2 (184)	155.7/97.6	— –12.1	— –13.1	

continued

TABLE 5-5 Continued

Reference	Subjects	Study Design	Potassium Intake,[b] g/d (mmol/d)
Overlack et al., 1991[a]	8 men 4 women	8-wk crossover	Placebo 4.7 (120) K citrate and bicarbonate
Cushman and Langford, 1988[a]	58 men	10-wk parallel	Placebo 3.1 (80) KCl supplement
Bulpitt et al., 1985[a]	15 men 18 women	12-wk parallel	Placebo 2.5 (64) KCl supplement
Chalmers et al., 1986[a]	91 men 16 women 90 men 15 women	12-wk parallel 12-wk parallel 	Normal diet High K 3.9 (100) Low Na 1.2–1.7 (50–75) High K 3.9 (100)
Grimm et al., 1988[a]	298 men	12-wk parallel	Placebo 3.8 (96) KCl supplement
Gu et al., 2001	60 men 90 women	12-wk parallel	Placebo 2.3 (60) KCL supplement
Siani et al., 1987[a]	23 men 14 women	15-wk parallel	Placebo 1.9 (48) KCl supplement
Obel, 1989[a]	21 men 27 women	16-wk parallel	Placebo 2.5 (64) potassium supplement
Peart et al., 1987[a]	269 men 215 women	24-wk parallel	Placebo 0.7–1.3 (17–34) KCl supplement

[a] Included in meta-analysis by Whelton et al. (1997).
[b] Potassium intake from diet unless otherwise indicated.
[c] Surrogate marker for electrolyte intake.
[d] If potassium supplement, then change in blood pressure compared to placebo.
SBP = systolic blood pressure, DBP = diastolic blood pressure.

Urinary Electrolytes,[c] g/d (mmol/d)		Mean Blood Pressure (mm Hg) Placebo or Control Diet	Mean Net Change in Blood Pressure[d] (mm Hg)		Comments
Potassium (K) g (mmol)	Sodium (Na) g (mmol)		SBP	DBP	
2.4 (62) 6.5 (167)	3.9 (169) 3.6 (156)	150/100	+2.8	+3.0	
1.9 (45) 4.4 (113)	Not given Not given	Not given/ 91.2	Not given	–0.1	
2.2 (55) 3.7 (95)	3.2 (139) 3.4 (149)	182/129	— +2.3	— +4.8	Subjects treated with antihypertensive medication
2.9 (75) 3.8 (96)	3.6 (156) 3.3 (145)	146.2/93.4	— –3.9	— –3.1	
2.9 (75) 3.4 (87)	1.9 (86) 1.7 (72)	143.1/89.2	— +1.0	— +1.6	
2.9 (76) 5.9 (150)	2.6 (114) 2.7 (116)	121.8/79.5	–0.2	–0.6	Subjects treated with antihypertensive medication
1.3 (34) 2.1 (54)	3.8 (164) 4.3 (185)	134/83	— –3.7	— –0.16	
2.2 (57) 3.4 (87)	4.2 (183) 4.3 (189)	145.8/92.5	— –14.0	— –10.5	
2.4 (62) 4.0 (102)	Not given	172/100	— –39.0	— –17.0	
Not given	Not given	133.5/84.9	— –0.8	— –0.7	Subjects treated with antihypertensive medication

cretion in each trial during follow-up and the corresponding net reduction in systolic ($p = 0.004$) and diastolic ($p = 0.003$) blood pressure. At higher levels of baseline 24-hour urinary sodium and of change in 24-hour urinary sodium, change in 24-hour urinary potassium showed a dose-response relationship with effect size for both systolic and diastolic blood pressure ($p < 0.01$). A similar graded response between change in 24-hour urinary potassium and effect size was observed at higher levels of 24-hour urinary sodium as follow-up for systolic ($p < 0.01$) but not for diastolic ($p = 0.2$) blood pressure (Whelton et al., 1997). This finding in the meta-analysis was evident in two 2 × 2 factorial trials (Chalmers et al., 1986; Skrabel et al., 1981). In both trials, supplemented potassium lowered blood pressure when sodium intake was high, but not when sodium intake was low.

The role of urinary sodium excretion as an effect modifier for the relationship between potassium consumption and blood pressure is consistent with results from observational investigations where blood pressure is more closely related to the ratio of urinary sodium:potassium excretion than to either urinary sodium or potassium excretion alone (Khaw and Barrett-Connor, 1988, 1990).

Treatment-related systolic blood pressure effect size estimates were significantly ($p = 0.03$) greater for the six trials with greater than 80 percent African-American participants compared with the 25 trials with greater than 80 percent white participants (Whelton et al., 1997). Also, there was some evidence for a dose-response relationship between potassium dose and blood pressure and some evidence for greater blood pressure reduction in African-American compared with white participants. In the two trials included that enrolled exclusively African-American individuals, potassium significantly lowered both systolic and diastolic blood pressure (Brancati et al., 1996; Obel, 1989). The blood pressure reductions in the study by Obel (1989) were particularly striking.

Overall, available evidence from observational studies, clinical trials, and meta-analyses of trials documents that higher intakes of potassium lower blood pressure. Blood pressure reductions from supplemental potassium occurred when baseline intake was low (e.g., 32 to 35 mmol/day in Brancati et al., 1996) and when baseline intake was much higher (> 80 mmol/day in Naismith and Braschi, 2003). Because virtually all trials used potassium chloride supplements, while observational studies assessed dietary potassium intake from foods (paired with nonchloride anions), the effects of potassium on blood pressure appear to result from potassium rather than its conjugate anion.

Prevention of Cardiovascular Disease

In addition to its blood pressure-reducing effects, increased potassium intake may have independent vascular protective properties. This possibility has been evaluated in experimental studies conducted in rodents over the last four decades. In a series of animal models, including both stroke-prone spontaneously hypertensive (SHRSP) and Dahl salt-sensitive rats, the addition of either potassium chloride or potassium citrate markedly reduced the mortality from stroke, a reduction that was unrelated to any measured attenuation of hypertension (Tobian, 1986; Tobian et al., 1984). In a more recent study with SHRSP rats in which aortic blood pressure was measured by continuous radiotelemetry, dietary potassium supplemented as either potassium bicarbonate or potassium citrate attenuated hypertension and prevented stroke (Tanaka et al., 1997). However, supplemental potassium chloride exacerbated hypertension, increased risk of stroke (Tanaka et al., 1997), and amplified renal microangiopathy (Tanaka et al., 2001), in comparison with potassium bicarbonate or citrate.

Hence, at least in this animal model, the anion accompanying potassium had a major qualitative effect on outcomes such that potassium citrate or bicarbonate was beneficial, while potassium chloride appeared to be harmful. Still, the discordant results between this study and the cited study of Tobian and coworkers (1984) are difficult to reconcile and therefore preclude firm conclusions.

An inverse relationship between dietary potassium intake at baseline and subsequent stroke-associated morbidity and mortality has also been noted in several, but not all, cross-sectional and cohort studies (Table 5-6). In a 12-year follow-up of 859 men and women enrolled in the Rancho Bernardo Study and who were 50 to 79 years of age at baseline, a significant ($p = 0.01$) inverse relationship between potassium intake and subsequent risk of stroke-related mortality was noted (Khaw and Barrett-Connor, 1987). Each standard deviation increase in potassium intake (0.4 g [10 mmol]/day) at baseline was associated with a 40 percent reduction in risk of stroke-related mortality relative risk (RR) = 0.6; 95 percent confidence interval (CI) = 0.44 to 0.81 after adjustment for age, gender, systolic blood pressure, caloric intake, and other potential confounders. Limitations of the study included the restricted characteristics of the cohort and the fact that the findings were based on only 24 stroke deaths. No significant relationship with coronary heart disease was detected.

Over a 16-year follow-up in the Honolulu Heart Study ($n = 7,591$

TABLE 5-6 Epidemiological Studies on Potassium Intake: Stroke and Heart Disease

Reference	Study Design
Stroke	
Khaw and Barrett-Connor, 1987	Rancho Bernardo Study, 12-yr follow-up *n* = 859 men and women, not energy adjusted
Lee et al., 1988	Honolulu Heart Study, 16-yr follow-up *n* = 7,591 Japanese men
Sasaki et al., 1995	Pearson correlation and multiple regression analysis *n* = 17 countries
Ascherio et al., 1998	Health Professionals Follow-up Study *n* = 43,738 men, multivariate analysis
Iso et al., 1999	Nurses' Health Study, prospective cohort *n* = 85,764 women, multivariate analysis

Potassium Intake,[a] g/d (mmol/d)	Results[b]	Other Results and Comments
Men	Rate of stroke/100	Multivariate regression analysis showed that a 0.39-g increase in daily potassium intake was associated with a 40 percent reduction in the risk of stroke-associated mortality.
T1 < 2.3 (59)	3.4	
T2 2.3–2.96 (59–76)	2.4	
T3 > 2.96 (76)	0.0	
	p trend = 0.16	
	RR T1 vs T3 = 2.6	
Women		
T1 < 1.9 (49)	5.3	
T2 1.9–2.57 (49–66)	2.1	
T3 > 2.6 (67)	0.0	
	p trend = 0.01	
	RR T1 vs T3 = 4.8	
	Incidence rate of fatal thromboembolic stroke	No significant correlation for nonfatal thromboembolic and fatal and nonfatal hemorrhagic strokes.
Q1 < 1.47 (38)	6.9	
Q2 1.47–1.86 (38–48)	5.3	
Q3 1.86–2.27 (48–58)	4.1	
Q4 2.27–2.77 (58–71)	2.4	
Q5 > 2.77 (71)	2.0	
	p = 0.002	
Potassium intake not reported	Urinary potassium correlated inversely with incidence of stroke mortality ($p < 0.05$)	
	RR of stroke	Risk for ischemic stroke alone was similar to risk for total strokes.
Q1 2.4 (61)	1.0	
Q2 3.0 (77)	0.85	
Q3 3.3 (85)	0.78	
Q4 3.6 (92)	0.76	
Q5 4.3 (110)	0.62	
	p trend = 0.007	

	RR of all strokes	RR of ischemic stroke
Q1 2.02 (52)	1.0	1.0
Q2 2.41 (62)	0.75	0.68
Q3 2.71 (69)	0.90	0.85
Q4 3.03 (78)	0.80	0.73
Q5 3.55 (91)	0.83	0.71
	p trend = 0.19	p trend = 0.07

continued

TABLE 5-6 Continued

Reference	Study Design
Fang et al., 2000	NHANES I study, 17-yr follow-up *n* = 9,866 men and women, not energy adjusted
Bazzano et al., 2001	NHANES I 19-yr follow-up n = 9,805 men and women, multivariate analysis
Green et al., 2002	4–8 yr follow-up 3,595 men and women, > 65 yr
Coronary heart disease	
Tunstall-Pedoe et al., 1997	Scottish Heart Health Study, prospective *n* = 11,629 men and women, 7.6 yr of follow-up

[a] T = tertile of intake, Q = quartile or quintile of intake.
[b] RR = relative risk, HR = hazard ratio, CHD = coronary heart disease.

Potassium Intake,[a] g/d (mmol/d)	Results[b]		Other Results and Comments
	RR of stroke mortality (T1 vs. T3)		Only among African-American men was lower dietary potassium intake a predictor of stroke mortality.
White men n = 3,169			
T1 < 2.0 (51)			
T2 2.0–2.88 (51–74)			
T3 > 2.88 (74)	1.66, p = 0.42		
African-American men n = 595			
T1 < 1.3 (33)			
T2 1.3–2.2 (33–56)			
T3 > 2.2 (56)	4.27, p = 0.0016		
African-American women n = 1,029			
T1 < 1.0 (26)			
T2 1.0–1.64 (26–42)			
T3 > 1.64 (42)	1.13, p = 0.53		
Nonhypertensive n = 7,632			
Males	1.23, p = 0.458		
Females	1.11, p = 0.415		
	HR of stroke	HR of CHD	
Q1 < 1.35 (35)	1.0	1.0	
Q2 1.35–1.94 (35–50)	0.75	1.04	
Q3 1.94–2.67 (50–68)	0.85	0.95	
Q4 > 2.67 (68)	0.76	1.01	
	p trend = 0.14	p trend = 0.93	
	HR = 1.28 when comparing Q1 to Q4, p < 0.0001		
	RR for stroke		
Q1 < 2.34 (59.8)	1.76		
Q2 2.35–2.92 (60–75)	1.22		
Q3 2.93–3.47 (75–89)	1.11		
Q4 3.48–4.16 (89–106)	1.37		
Q5 > 4.17 (107)	1.0		
Potassium intake not reported			Potassium excretion was inversely correlated with incidence of CHD and all deaths

Japanese-American participants), there was a significant inverse relationship ($p = 0.002$) between potassium intake and mortality from thromboembolic stroke (Lee et al., 1988). No significant association was noted for nonfatal thromboembolic stroke or for fatal or nonfatal hemorrhagic strokes. Additionally, inverse relationships between potassium intake and stroke mortality were noted in several cohort studies (Sasaki et al., 1995; Xie et al., 1992; Yamori et al., 1994) but these findings were not adjusted for caloric intake and/or were based on an ecologic analysis (Xie et al., 1992). In a 7-year follow-up report of 5,754 men and 5,875 women who were participants in the Scottish Heart Health Study, an inverse relationship between potassium intake and subsequent death, both from all causes and from coronary heart disease, was found (Tunstall-Pedoe et al., 1997).

Similarly, over the course of 8 years of follow-up in 43,738 U.S. men in the Health Professionals Study, there was a significant inverse relationship between baseline potassium intake and stroke ($p = 0.007$ for trend across quintiles of potassium intake) after adjustment for established cardiovascular disease risk factors, including blood pressure and caloric intake (Ascherio et al., 1998). The multivariate RR of stroke for men in the highest versus lowest quintile of potassium intake was 0.62 (95 percent CI = 0.43–0.88). The association was similar for both ischemic ($n = 210$) and all ($n = 328$) strokes. Use of potassium supplements was also inversely associated with the risk of stroke.

In a 14-year study of 85,764 U.S. women who participated in the Nurses Health Study, there was an inverse relationship between potassium intake and ischemic stroke (RR = 0.72; 95 percent CI = 0.51 to 1.01 for comparison of upper and lower quintiles of potassium intake; 347 strokes occurred during this time period), but much of the association was lost following adjustment for calcium intake (Iso et al., 1999). Two analyses of NHANES I follow-up study have been reported. In a 17-year analysis of subsequent stroke mortality in approximately 10,000 men and women (during which there were 304 strokes), there was a significant inverse relationship between potassium intake and stroke mortality in hypertensive and African-American men, but not in other subgroups (Fang et al., 2000). In a 19-year follow-up of the same cohort, the relationships of potassium intake with fatal and nonfatal strokes (total $n = 927$) and coronary heart disease ($n = 1847$) events were assessed (Bazzano et al., 2001). Overall, stroke hazard was significantly different among quartiles of potassium intake ($p = 0.03$), but the relationship was nonlinear. Participants in the lowest quartile of potassium intake at baseline

(< 1.4 g [34.6 mmol]/day) experienced a 28 percent higher risk of stroke (95 percent CI = 1.11 to 1.47; e.g., $p < 0.0001$) compared with the remainder of the cohort after adjustment for established cardiovascular disease risk factors.

Prevention of Bone Demineralization

Epidemiological Studies

Observational studies suggest that increased fruit and potassium consumption is associated with increased bone mineral density (BMD) (see Table 5-7). Pyridinoline excretion, a marker of bone resorption, was negatively associated with energy-adjusted potassium intakes (New et al., 2000). Longitudinal studies have documented that potassium intake was positively associated with BMD at various sites (Macdonald et al., 2004; Tucker et al., 1999).

Given that net endogenous acid production (NEAP) can be closely estimated by the dietary protein-to-potassium ratio (Frassetto et al., 1998), these observations are those predicted if sustained high rates of diet-induced endogenous acid act over time to demineralize bone. The association of NEAP with several indices of skeletal status in 1,056 pre- and perimenopausal women was recently reported (New et al., 2004). Lower estimates of energy-adjusted NEAP were correlated with higher BMD at the spine and hip, as assessed by dual X-ray absorptiometry. Hip and forearm bone mass decreased significantly across increasing quartiles of NEAP. These differences remained significant when adjusted for age, weight, height, and menstrual status. Lower estimates of NEAP were correlated with lower urinary excretion of deoxypyridinoline, a marker of bone resorption, and were significant predictors of spine and forearm bone mass (New et al., 2004).

Intervention Studies

Two studies have been reported in which supplemental potassium was provided and subsequent measures of calcium and phosphorus balance were evaluated. In a study of 18 healthy postmenopausal women (Sebastian et al., 1994), supplemental potassium bicarbonate provided for 18 days induced a slight but sustained and near immediate increase in the plasma bicarbonate concentration and blood pH and virtually abolished net renal acid excretion. Calcium and phosphorus balance improved (as measured by the difference between dietary intake and fecal/urine excretion). There was also

TABLE 5-7 Epidemiological Studies on the Effect of Potassium Intake on Bone Mineral Density (BMD)

Reference	Study Design	Effect	Findings
New et al., 1997	Cross-sectional 944 women	+	Potassium intake was significantly ($p < 0.05$) correlated with BMD for lumbar spine, femoral neck, trochanter, and Ward's area in premenopausal women
Tucker et al., 1999	Cross-sectional and longitudinal 907 men and women	+	Potassium intake was significantly ($p < 0.05$) associated with BMD for the femoral neck, trochanter, Ward's area, and radius in men (cross-sectional) In women potassium intake was significantly ($p < 0.05$) associated with bone mineral density for the trochanter, Ward's area, and radius (cross-sectional) In a 4-yr analysis of change in BMD, potassium intake was significantly ($p < 0.05$) associated with less decline in BMD for femoral neck and trochanter in men
New et al., 2000	Cross-sectional 62 women	+	Potassium intake was significantly ($p < 0.01$) associated with higher total bone mass ($p < 0.05$ to $p < 0.005$) Potassium intake was significantly ($p < 0.02$) and negatively associated with pyridinoline excretion and deoxypyridinoline excretion
Jones et al., 2001	Cross-sectional 330 children	+	Significant ($p < 0.001$) association between urinary potassium, femoral neck, lumbar spine, and total body BMD in prepubertal children
Macdonald et al., 2004	Longitudinal 891 women	+	Significant ($p < 0.05$) and positive correlation between potassium intake and femoral neck BMD in premenopausal and perimenopausal women

TABLE 5-7 Continued

Reference	Study Design	Effect	Findings
New et al., 2004	Cross-sectional 1,056 women	+	Diets with lower estimates of net endogenous acid production (NEAP) (higher dietary intake of potassium and lower dietary protein) were significantly ($p < 0.02$–0.05) correlated with BMD in the hip and spine and greater forearm mass A significant ($p < 0.05$) correlation was found between lower estimates of NEAP and lower excretion of deoxypyridinoline

NOTE: + means potassium had a significant impact on BMD.

a reduction in the urinary excretion of hydroxyproline, a marker of bone breakdown, and an increase in the serum concentration of osteocalcin, a marker of bone formation. When supplemental potassium bicarbonate was discontinued, the levels of plasma bicarbonate and arterial pH, like those of all other measured variables that had changed with the supplement, returned almost immediately to levels nearly identical to those occurring before the potassium bicarbonate was supplemented. This pattern of results suggests that a state of low-grade metabolic acidosis existed immediately before and after potassium bicarbonate was supplemented; that the acidosis resulted from the endogenous generation of noncarbonic acid at a rate greater than that at which the kidney could excrete it; that the acidosis induced increased bone resorption and reduced bone formation; that the acidosis induced increased renal loss of calcium and phosphate and thereby negative balances of both; and that supplemental potassium bicarbonate reversed each of these metabolic derangements by fully correcting the low-grade metabolic acidosis by titrating endogenously produced noncarbonic acid. Similar results were seen and conclusions drawn in metabolic studies of nonhypertensive young men and women in whom dietary potassium chloride was replaced with potassium bicarbonate, whereupon the urinary excretion of deoxypyridinoline, pyridinoline, and n-telopeptide (markers of bone resorption) promptly decreased (Maurer et al., 2003).

In a pre- and poststudy in which 21 adult patients with calcium urolithiasis were treated with potassium citrate for 11 to 120 months,

spinal BMD substantially increased over a period of time (which varied from approximately 1 to 10 years) in which an age-related decrease might otherwise have occurred (Pak et al., 2002). In normal adults, potassium bicarbonate has been demonstrated to be hypocalciuric, whereas potassium chloride has not (Lemann et al., 1991). This reflects not only the direct acidosis-countering effect of the bicarbonate component of potassium bicarbonate, but also the capacity of potassium (Brunette et al., 1992) and bicarbonate (Peraino and Suki, 1980) to jointly enhance the renal reclamation of calcium.

Relationship with Sodium

The dietary intake of sodium chloride is an important determinant of urinary calcium excretion and calcium balance. The urinary excretion of calcium is well documented to vary directly with that of sodium (see Table 6-19 in Chapter 6). There is evidence that reducing dietary sodium chloride can induce beneficial effects on bone by reducing the renal loss of calcium and increasing its retention (Devine et al., 1995; Matkovic et al., 1995). However, on a mole-for-mole basis, the hypocalciuric effect of orally administered potassium overrides the hypercalciuric effect of dietary sodium (Morris et al., 1999b; Sellmeyer et al., 2002). In a metabolically controlled outpatient study of normal men fed a diet deficient in potassium (1.2 g [30 mmol]/day), increasing dietary sodium chloride from 1.8 g (30 mmol)/day to 14.6 g (250 mmol)/day induced a 50 percent increase in urinary calcium that supplemental potassium bicarbonate either reversed or abolished, depending on whether dietary potassium was increased to 2.7 or 4.7 g (70 or 120 mmol)/day (Morris et al., 1999b). In an outpatient study of postmenopausal women, the hypercalciuric effects of sodium loading with 5.2 g (225 mmol)/day sodium and a concomitant increase in bone resorption, as indicated by biochemical markers, was abolished by supplying 3.5 g (90 mmol)/day of dietary potassium as potassium citrate, a supplement that increased urinary potassium to 141 mmol (5.5 g)/day (Sellmeyer et al., 2002).

Prevention of Kidney Stones

Epidemiological Evidence

In several studies, an increased dietary intake of potassium has been associated with a reduced risk of kidney stones. The occur-

rence of kidney stones in both sexes is directly related to the urinary sodium:potassium ratio (Cirillo et al., 1994). In a pre-post, uncontrolled study of children with idiopathic hypercalciuria, reducing the dietary sodium:potassium ratio greatly reduced urinary calcium excretion (Alon and Berenbom, 2000). Hypercalciuria is generally accepted as a major risk factor for calcium-containing kidney stones (Coe et al., 1992). The incidence of kidney stones has been shown to increase with an increased sodium:potassium ratio (Stamler and Cirillo, 1997).

In a longitudinal study of 51,529 men conducted prospectively over 4 years, the incidence of symptomatic kidney stones, while not correlating with dietary sodium, did correlate strongly and negatively with dietary potassium as measured by a food-frequency questionnaire over a broad range of intake (2.9 to 4.0 g [74 to 102 mmol]/day) (Curhan et al., 1993) (see Table 5-8). The absence of a relationship between dietary sodium and kidney stones should be

TABLE 5-8 Epidemiological Studies on Potassium Intake and Risk of Kidney Stone Formation

Reference	Study Design	Potassium Intake,[a] g/d (mmol/d)	Relative Risk for Kidney Stones
Curhan et al., 1993	Health Professionals Study, 45,619 men, 4-yr follow-up	Q1 < 2.9 (74) Q2 3.1 (79) Q3 3.4 (87) Q4 3.8 (97) Q5 > 4.0 (102)	1.0 0.88 0.74 0.69 0.49 p trend < 0.001
Curhan et al., 1997	Nurses' Health Study, 91,731 women, 12-yr follow-up	Q1 2.0 (52) Q2 2.7 (69) Q3 3.2 (81) Q4 3.7 (95) Q5 4.7 (119)	1.0 0.86 0.75 0.67 0.65 p trend < 0.001
Hirvonen et al., 1999	Prospective cohort, n = 27,001 Finnish male smokers	Q1 3.8 (97) Q2 4.6 (118) Q3 5.1 (131) Q4 5.7 (146)	1.0 0.76 0.85 0.79 p trend = 0.34

[a] Q = quartile or quintile of intake.

interpreted cautiously because the food-frequency questionnaire used in these studies did not measure sodium intake either accurately or precisely (Subar et al., 2001). In this study (Curhan et al., 1993), the incidence of kidney stones correlated directly with meat intake. In a 12-year prospective study of an even larger number of female nurses, the incidence of stone formation was inversely associated with dietary potassium (2.0 to 4.7 g [52 to 119 mmol]/day) (Curhan et al., 1997). In a study conducted in Finland where the dietary potassium intake is greater than in the United States, risk for kidney stones appeared to decrease with an increased intake of potassium (3.8 compared with 4.6 g [97 to 118 mmol]/day) (Hirvonen et al., 1999). However, higher intakes of potassium did not appear to further reduce risk, and the relationship between potassium intake and kidney stones, overall, was nonsignificant.

Role of Acid-Base Balance, Urinary Citrate, and Relationship with Sodium

An increased intake of meat has long been recognized as a risk factor for kidney stones, presumably because of the resultant acid load and the well-documented impact of that load on urinary calcium excretion (Lemann, 1999; Lemann et al., 2003). By increasing the acid load and slightly reducing the plasma bicarbonate concentration, an increased intake of animal protein also induces a decrease in the urinary excretion of citrate (Breslau et al., 1988), a major risk factor for the formation of kidney stones (Coe et al., 1992; Pak, 1987). Urinary citrate chelates urinary calcium in a soluble form (Bisaz et al., 1978; Meyer and Smith, 1975; Pak, 1987). Both hypocitraturia and hypercalciuria occur with even modest potassium deficiencies (Hamm, 1990; Simpson, 1983). Administration of either potassium bicarbonate or potassium citrate induces an increase in the urinary excretion of citrate (Pak, 1987; Sakhaee et al., 1991; Simpson, 1983), as well as a reduction in the urinary excretion of calcium (Lemann et al., 1989, 1991). Neither the citraturic effect of potassium citrate nor its hypocalciuric effect is greater than that of potassium bicarbonate, presumably because these salts induce similarly small increases in the plasma concentration of bicarbonate (Sakhaee et al., 1991).

One clinical trial tested the effects of potassium citrate in preventing recurrent kidney stones (Barcelo et al., 1993). In a double-blind, placebo-controlled trial of 57 patients (25 men and 32 women) with kidney stones and hypocitraturia conducted over 3 years, 1.2 to 2.3 g (30 to 60 mmol) of potassium citrate were administered in addition

to the usual diet. This regimen induced a highly significant reduction in the occurrence of kidney stones. The stone formation rate was significantly lower in the potassium citrate group than in the control group (0.1 stone/patient-year versus 1.1 stones/patient-year, $p < 0.001$). Total urinary excretion of potassium in the 18 subjects in the potassium citrate group averaged 105 mmol (4.1 g)/day after 36 months, compared with their baseline average of 61 mmol (2.4 g)/day (Barcelo et al., 1993). While not directly measured, it is thus assumed that 2.4 g (61 mmol) would have been present in the diets consumed, for a total intake with the supplement of around 3.6 to 4.7 g (90 to 120 mmol). Similar results have been recorded in uncontrolled studies of potassium citrate (Pak and Fuller, 1986; Pak et al., 1985, 1986; Preminger et al., 1985).

Overall, evidence from several prospective observational studies and one clinical trial supports the use of kidney stones as an outcome criterion to establish dietary adequacy of potassium. However, additional trials are clearly warranted.

Prevention of Impaired Pulmonary Function

Changes in the extracellular and intracellular concentration of electrolytes, including potassium, can influence the contraction and relaxation of bronchial smooth muscles (Souhrada and Souhrada, 1983, 1984). The limited studies on potassium intakes and pulmonary function in adults have yielded mixed results, with one study showing increased airway responsiveness to chemicals that induce constriction of the airways (e.g., histamine) with decreasing urinary potassium excretion (Tribe et al., 1994), while no relationship was found between potassium intake and bronchial responsiveness or respiratory symptoms in adults in a second study (Zoia et al., 1995).

As in adults, data on children are limited. Increased bronchial responsiveness with higher levels of potassium excretion was observed in the children studied (Pistelli et al., 1993), while in another study, low potassium intakes were associated in children with lower pulmonary function (e.g., expiratory volume, flow, and capacity) (Gilliland et al., 2002).

FACTORS AFFECTING POTASSIUM REQUIREMENTS

Climate and Physical Activity

Increased losses of potassium, primarily via sweat, can occur with heat exposure and exercise. Thus the requirement for potassium

will increase in both situations. The potassium concentration in sweat is approximately 4 to 5 mmol (0.2 g)/L. This concentration can increase up to 14 mmol (0.5 g)/L upon thermal exposure (Fukumoto et al., 1988). The sweat potassium concentration in heat-acclimatized individuals exposed to heat stress (40°C [104°F]) was approximately 5.4 mmol (0.2 g)/L, and total sweat loss was approximately 11 L/day, yielding a total potassium sweat loss of approximately 60 mmol (2.3 g)/day while consuming a diet providing 3.8 g (97 mmol)/day (Malhotra et al., 1976). When total estimated losses (sweat + urine) were summed (estimating sweat volume of 8 L/day), the maximum loss was equivalent to 116 mmol (4.5 g)/day, which exceeded the potassium intake. Average sweat potassium daily losses of three men who were exposed to 37.8°C (100°F) heat for 7.5 hours per day for 16 days fell from 79 mmol (3.1 g) measured on day 2 to 14 mmol (0.55 g) by day 11. Hence, there was a decline in sweat loss over time, demonstrating that acclimation occurred and suggesting that potassium balance might be achieved over a short period of time.

The effects of 90 minutes of heat exposure (46°C [117°F]) without exercise during low (0.78 to 1.2 g [20 to 30 mmol]/day) and high (7.8 g [200 mmol]/day) sodium intakes on a number of parameters, including plasma potassium concentrations, were studied in eight healthy volunteers (20 to 28 years of age) (Follenius et al., 1979). There were significant changes in plasma potassium concentrations whether the subjects were on a low or high sodium diet. Plasma potassium concentrations ranged from about 3.97 to 4.15 mmol/L.

Seven healthy men, 18 to 23 years of age, were exposed to 40°C (104°F) heat in a controlled heat chamber and to exercise (Fukumoto et al., 1988). Sweat potassium concentration was 11.3 ± 3.1 mmol/L during the running exercise compared with 14.2 ± 4.6 mmol/L during thermal exposure (40°C). Conversely, sweat sodium losses were greater during the running exercise (123.1 ± 33.6 mmol/L) compared with the heat exposure (84.3 ± 31.5 mmol/L).

Approximately 1.2 g (32 mmol)/day of potassium losses from sweat were observed during 6 hours of intermittent treadmill activity in a 40°C environment in 12 unacclimatized men (Armstrong et al., 1985). No significant changes in serum potassium concentrations in 10 experienced male marathon runners were seen after they completed three 20-mile runs under three different fluid replacement treatments (water, electrolyte-glucose solution, or a caffeine solution [5 mg of caffeine/kg of body weight]) (Wells et al., 1985). Pre-exercise serum potassium concentrations were about 4.4

mmol/L for all three trials, and averaged about 4.9 mmol/L for all three trials postexercise (Wells et al., 1985). Hence, under these three conditions, a potassium deficit was not evident.

The effects of two diets and exercise on potassium losses were evaluated in eight men during two 4-day exercise-dietary regimens (Costill et al., 1982). The control diet contained 3.1 g (80 mmol)/day of potassium, while the experimental diet contained only 0.98 g (25 mmol)/day of potassium. Urinary potassium excretion was significantly lower with the low potassium diet (2.6 versus 1.2 g [67 versus 31 mmol]/day) on day 5 of the study for each dietary period. Sweat potassium also significantly decreased from 12.3 to 10.9 mmol/day (measured on day 1 of the study for each dietary period). When fed 3.1 g (80 mmol)/day, the individuals were in balance, whereas a negative potassium balance was observed (–0.5 g [–14 mmol]/day) when fed the low potassium diet. Still, the authors did not detect diminished total body potassium content with a combination of heavy exercise and the lower potassium diet. However, this dietary and exercise regimen was brief; the long-term effects are uncertain.

Diuretics

Diuretics, which are often prescribed for the treatment of hypertension and congestive heart failure, result in increased urinary excretion of potassium and can lead to hypokalemia. However, the response is highly dose-dependent. Continual loss of potassium, if sustained, can result in clinical signs and symptoms of potassium deficiency, including arrhythmias (Robertson, 1984). For this reason, potassium supplements are often prescribed. In a recently completed trial (Furberg et al., 2002), approximately 8 percent of individuals assigned to the thiazide diuretic, chlorthalidone (12.5 to 25 mg/day), required a potassium supplement as treatment for diuretic-induced hypokalemia. Alternatively, potassium-sparing diuretics (e.g., amiloride, triamterene, and spirolactones) are frequently used concurrently with thiazide-type diuretics, which increase urinary potassium excretion. Triamterene has been shown to prevent diuretic-induced potassium loss comparable to 3.1 to 4.7 g (80 to 120 mmol)/day of supplemental potassium. While diuretics can cause hypokalemia, the amount of additional potassium required to prevent hypokalemia is uncertain and highly variable. Accordingly, in individuals taking diuretics, serum potassium should be regularly checked by their health care provider.

Forms of Potassium

The anions that accompany potassium have metabolic and physiologic properties that influence health. Plant foods rich in potassium, like fruits and nongrain vegetables, are also rich in bicarbonate-yielding precursors like citrate. In contrast, plants contain little chloride. In fact, chloride, like sodium, is ingested almost entirely as sodium chloride, primarily in processed foods and in discretionary use during cooking for seasoning. In the present Western diet, which dates from the Industrial Revolution some 200 years ago, the content of sodium and chloride is not only much higher than that of previous diets, but the contents of both potassium and bicarbonate-yielding substances are also much lower (Eaton et al., 1999; Morris RC et al., 2001; Sebastian et al., 2002). Thus most dietary deficiencies of potassium are accompanied by a relative lack of bicarbonate precursors. With the advent of the Western diet, both the potassium:sodium ratio and the bicarbonate:chloride ratio have become reversed.

Potassium is also consumed as potassium chloride as a food additive ingredient, a salt substitute, or as pills used therapeutically to treat diuretic-induced hypokalemia. While potassium chloride can correct hypokalemia and reduce blood pressure (see Tables 5-4 and 5-5), it cannot correct the low-grade metabolic acidosis induced by modern diets because chloride, in contrast to bicarbonate precursors, does not titrate diet-derived acids.

In healthy adults, potassium bicarbonate increased excretion of citrate and decreased calcium, whereas potassium chloride did not (Lemann et al., 1991; Sakhaee et al., 1991), suggesting that potassium bicarbonate or citrate is the form most conducive to a reduced risk of kidney stones. Because diet-derived acid can result in bone demineralization (Bushinsky and Frick, 2000; Lemann et al., 1966; New et al., 2000) as illustrated in Figure 5-2, the nonalkaline potassium chloride would not be expected to promote bone health as would be predicted with potassium bicarbonate (Lemann et al., 1991, 1993).

Interactions with Other Electrolytes

The effects of potassium intake depend, in part, on the level of sodium chloride intake (and vice versa). Previous sections have documented that potassium blunts the effect of sodium chloride on blood pressure—that an increased intake of potassium bicarbonate or other bicarbonate-yielding potassium salts mitigates salt sensitiv-

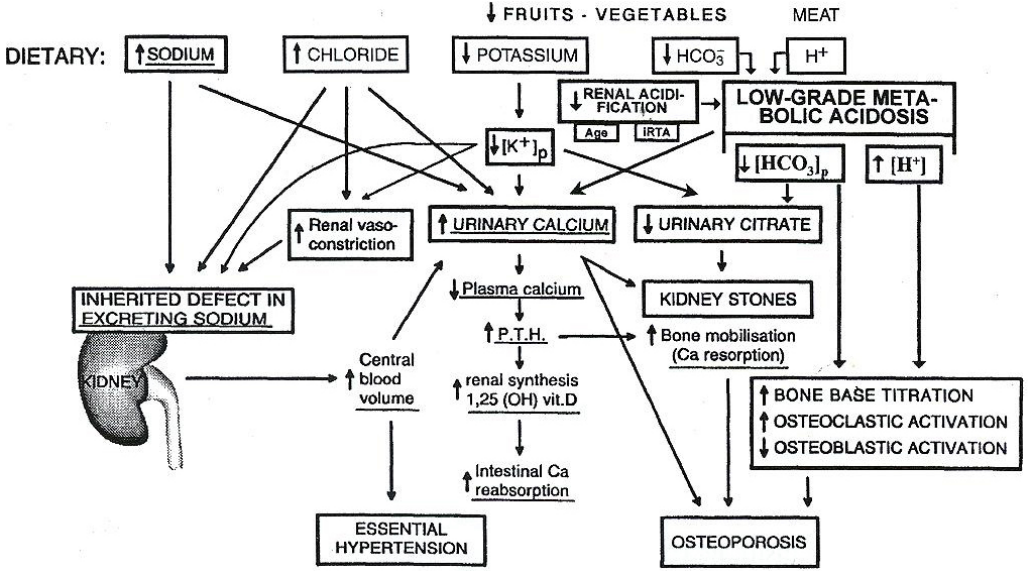

FIGURE 5-2 Hypothesized relationships between certain dietary inorganic electrolytes and bicarbonate, the kidney, essential hypertension, kidney stones, and osteoporosis: the modern diet's excessive dietary sodium and chloride and deficient dietary potassium and bicarbonate precursors as determinants of both low-grade metabolic acidosis and hypercalciuria and thereby osteoporosis and kidney stones. As formulated, the acidosis can be amplified by impaired renal acidification that occurs as part of the "incomplete syndrome of renal tubular acidosis" (IRTA), an age-related decline in renal function ("age"), or both. The underlined dietary determinants and pathogenic events are those originally hypothesized and depicted. In this scheme, the word "osteoporosis" replaces the term "bone mineralization" specified in the depiction of the original formulation (Modified from MacGregor and Cappuccio [1993] by Morris RC et al. [2001]). Reprinted with permission from Morris RC et al. (2001). Copyright 2001 by Elsevier.

ity and lowers urinary calcium excretion. At higher levels of sodium chloride intake, potassium reduces blood pressure to a greater extent than at lower levels of sodium chloride intake (Whelton et al., 1997). While the relationship of kidney stones with urinary potassium excretion was weak and nonsignificant, the relationship of kidney stones to the urinary sodium: potassium ratio was direct and highly significant (Cirillo et al., 1994). Finally, the hypocalciuric effect of supplemental dietary potassium bicarbonate is also dampened by dietary sodium chloride (Sellmeyer et al., 2002).

Given the interrelatedness of sodium and potassium, the requirement for potassium may well depend on the level of dietary sodium, and the deleterious effects of sodium may be attenuated by higher dietary intakes of potassium. However, data are presently insufficient to set different potassium intake recommendations according to the level of sodium intake, and vice versa. Likewise, data are insufficient to set requirements based on the sodium: potassium ratio.

Race

As previously discussed, sodium chloride raises blood pressure to a greater extent in African-American men than in white men (Morris et al., 1999b; Weinberger, 1996) and the expression of salt sensitivity is modulated by dietary potassium (Morris et al., 1999b; Weinberger et al., 1982). In one trial (Morris et al., 1999b; Figure 5-1), salt sensitivity continued among some of the nonhypertensive African-American men who consumed a high-normal level of potassium (4.7 g [120 mmol]/day). In another study of African Americans, most of whom were nonhypertensive, a higher dietary intake of potassium (6.6 g [170 mmol]/day) as potassium bicarbonate abolished salt sensitivity (Schmidlin et al., 1999).

Available data also suggest that African Americans, compared with their white counterparts, are more sensitive to the blood pressure-reducing effects of increased dietary potassium. A significant reduction in systolic and diastolic blood pressure was seen when African-American individuals, most of whom were nonhypertensive, increased dietary potassium from a level of 1.3 to a level of 3.1 g (33 to 80 mmol)/day (Brancati et al., 1996). In another study that enrolled African-American hypertensive subjects, supplementation with 2.5 g (64 mmol)/day of potassium chloride significantly reduced systolic and diastolic blood pressure (Obel, 1989). However, neither of these trials enrolled white participants, so the extent of blood pressure reduction in African Americans from increased po-

tassium intake cannot be directly compared with that of non-African Americans. The Dietary Approaches to Stop Hypertension (DASH) trial tested the effects of a diet high in fruits and vegetables (and thus also higher levels of potassium, magnesium, and fiber) in both African Americans and non-African Americans (Appel et al., 1997; see Table 5-4). While blood pressure was reduced in both groups, only the reductions in African Americans achieved statistical significance. Such evidence must be interpreted cautiously because the diet emphasized several nutrients besides potassium. The potential for race or ethnicity to modify the effects of potassium on kidney stone formation and metabolic bone disease has not been well studied. Overall, there is insufficient evidence at this time to set different potassium recommendations based on race or ethnicity.

FINDINGS BY LIFE STAGE AND GENDER GROUP

Infants Ages 0 Through 12 Months

Evidence Considered in Setting the AI

The health effects of potassium intake in infants are uncertain. Thus recommended intakes of potassium are based on an Adequate Intake (AI) that reflects a calculated mean potassium intake of infants principally fed human milk, or a combination of human milk and complementary foods.

Ages 0 Through 6 Months. Using the method described in Chapter 2, the AI for potassium for infants ages 0 though 6 months is based on the average amount of potassium in human milk that is consumed. A mean intake of 0.39 g/day of potassium is estimated based on the average volume of milk intake of 0.78 L/day (see Chapter 2) and an average concentration of potassium in human milk of 0.5 g/L during the first 6 months of lactation (see Table 5-9). An AI of 0.4 g/day of potassium is set for infants 0 through 6 months of age, after rounding.

Ages 7 Through 12 Months. The potassium intake for older infants can be determined by estimating the intake from human milk (concentration × 0.6 L/day) and complementary foods (see Chapter 2). Potassium intake (n = 51) from complementary foods was estimated to average 0.44 g/day based on data from the Continuing Survey of Food Intakes of Individuals (CSFII) (see Appendix Table E-4). The average intake from human milk is approximately 0.3 g/

TABLE 5-9 Potassium Content in Human Milk

Reference	Study	Stage of Lactation[a]	Potassium Concentration (g/L)[b]
Gross et al., 1980	18 women	1 mo pp	0.59
Picciano et al., 1981	26 women	1 mo pp	0.46
		2 mo pp	0.42
		3 mo pp	0.41
Keenan et al., 1982	14 women	3.5–6 wk pp	0.59
		8.5–18 wk pp	0.54
		20–32 wk pp	0.52
Lemons et al., 1982	7 women	1 mo pp	0.53
		1.5 mo pp	0.56 preterm
		> 2 mo pp	0.53 preterm
Dewey and Lonnerdal, 1983	20 women	1 mo pp	0.53
		2 mo pp	0.48
		3 mo pp	0.47
		4 mo pp	0.46
		5 mo pp	0.46
		6 mo pp	0.43

[a] pp = postpartum.
[b] All values except those from mothers with preterm infants were averaged together to derive average potassium content of human milk = 0.5 g/L.

day (0.5 g/L × 0.6 L/day). Thus the total potassium intake is estimated to be 0.74 g/day (0.3 g/day + 0.44 g/day). Therefore, the AI is 0.7 g (18 mmol)/day of potassium, after rounding.

Potassium AI Summary, Ages 0 Through 12 Months

AI for Infants
0–6 months 0.4 g (10 mmol)/day of potassium
7–12 months 0.7 g (18 mmol)/day of potassium

Children and Adolescents Ages 1 Through 18 Years

Evidence Considered in Setting the AI

Direct evidence on the potassium requirements of children is lacking. Blood pressure is one potential indicator; however, few studies

have assessed the relationship of potassium intake with blood pressure or its rise during childhood and adolescence. In one prospective observational study of 233 Dutch children aged 5 to 17 years, the rise in blood pressure over 7 years was significantly and inversely associated with dietary potassium intake and the dietary sodium:potassium ratio, as estimated from multiple overnight urine collections (Geleijnse et al., 1990). Two small trials tested the effects of potassium supplementation in children (Miller et al., 1987; Sinaiko et al., 1993). In both trials, potassium had no significant effect on blood pressure; however, statistical power may have been inadequate.

Because the conditions resulting from potassium deficiency (i.e., elevated blood pressure, bone demineralization, and kidney stones) are chronic and likely result from inadequate intake over an extended period of time, including childhood, it is appropriate to extrapolate recommended intakes of potassium in adults to children. However, the optimal approach to extrapolation is uncertain (e.g., adjustment based on weight, energy intake, or another method). Adjustment based on energy intake was deemed most appropriate because of concern that adjustment based on weight might lead to a relatively low and potentially inadequate intake of potassium. Furthermore, given the high energy intake of children relative to their weight and the potential for a high sodium intake as a result of their high energy intake, a greater intake of dietary potassium would be appropriate as a means to mitigate the adverse effects of sodium.

The AI is thus derived by extrapolating from the adult AI on the basis of the average of median energy intake levels. Based on data from CSFII, the median energy intake for 1- to 3- and 4- to 8-year-old children is 1,372 and 1,759 kcal/day, respectively (IOM, 2002). Median energy intakes for preadolescent (9 to 13 years of age) and adolescent (14 to 18) boys and girls range from 1,877 to 2,226 and 1,872 to 2,758 kcal/day, respectively.

Potassium AI Summary, Ages 1 Through 18 Years

AI for Children	
1–3 years	**3.0 g (77 mmol)/day of potassium**
4–8 years	**3.8 g (97 mmol)/day of potassium**
AI for Boys	
9–13 years	**4.5 g (115 mmol)/day of potassium**
14–18 years	**4.7 g (120 mmol)/day of potassium**

AI for Girls	
9–13 years	**4.5 g (115 mmol)/day of potassium**
14–18 years	**4.7 g (120 mmol)/day of potassium**

Adults Ages 19 Through 50 Years

Evidence Considered in Setting the AI

In clinical trials, potassium chloride has been shown to reduce blood pressure (Cappuccio and MacGregor, 1991; Geleijnse et al., 2003; Whelton et al., 1997); potassium bicarbonate has been shown to reduce the rise in blood pressure in response to increased sodium chloride intake (salt sensitivity) (Morris et al., 1999b); and potassium citrate has been shown to reduce the risk of kidney stones (Barcelo et al., 1993) (see earlier section, "Indicators Considered for Estimating the Requirement for Potassium"). Observational studies suggest that diets rich in potassium may also prevent bone disease and cardiovascular disease, particularly stroke.

Dose-response trials that test the effect of at least three levels of potassium are not available. While such studies would be useful in trying to estimate an average requirement (an EAR) based on blood pressure, substantial reductions in blood pressure in nonhypertensive individuals were observed at total dietary potassium intakes ranging from around 3.1 to 4.7 g (80 to 120 mmol)/day (Table 5-4). One dose-response trial tested the effect of potassium on salt sensitivity; in this study, an intake of 4.7 g (120 mmol)/day of potassium as potassium bicarbonate abolished severe sodium sensitivity in most nonhypertensive African-American men, a degree of salt sensitivity not observed in white men also tested (Morris et al., 1999b) (see Figure 5-1). In white men enrolled in this trial, salt sensitivity was reduced at a potassium intake of 2.7 g (70 mmol)/day compared with a potassium intake of 1.2 g (30 mmol)/day. Finally, three epidemiological studies suggest that increasing potassium intakes may reduce the risk of kidney stones (Table 5-8) (Curhan et al., 1993, 1997; Hirvonen et al., 1999). At the highest quintile of potassium intake in two studies conducted in the United States (4.0 and 4.7 g [102 and 120 mmol]/day), the lowest relative risk of kidney stones was observed (RR 0.49 and 0.65) (Curhan et al., 1993, 1997). In Finland where potassium intakes are greater than in the United States or Canada (Rose et al., 1988), at the second quartile of intake (4.6 g [118 mmol]/day), there was a reduced relative risk of kidney stones (0.76) that was not further reduced at higher potassium intakes (Hirvonen et al., 1999).

The trial data are nonetheless insufficient for setting an EAR, which would require data at multiple intake levels so that a level could be derived that would reduce blood pressure, mitigate salt sensitivity, or decrease the risk of kidney stones in 50 percent of individuals evaluated. Still, it is possible to set an AI at 4.7 g (120 mmol)/day using available data.

While the AI is set at the same intake level for men and women, it is recognized that differences in body size, body composition, and caloric intake may affect requirements. However, presently available data are insufficient to set gender-specific requirements. Since most of the studies used to derive the AI included both men and women and did not report findings on the basis of these characteristics, it is thus appropriate at this point to set the recommended intake at the same level of intake for both.

It should be recognized that the studies used to set the AI were conducted in the setting of a high sodium intake (2.7 to 5.7 g [117 to 13 mmol]/day), which greatly exceeds the AI of 1.5 g (65 mmol)/day of sodium. While it is plausible that the AI for potassium might be lower in the setting of a reduced sodium intake, data are insufficient to set this level.

Summary. The AI for potassium is set at 4.7 g (120 mmol)/day based on blunting the severe salt sensitivity prevalent in African-American men and decreasing the risk of kidney stones, as demonstrated in a 3-year double-blind controlled study. Blood pressure studies in nonhypertensive individuals (Table 5-3) are supportive of this level of intake as a means to lower blood pressure. Epidemiological studies also suggest that higher levels of potassium intake from foods are associated with decreased bone loss. It is important to note that the beneficial effects of potassium in these studies appears to be mainly from the forms of potassium that are associated with bicarbonate precursors—the forms found naturally in foods such as fruits and vegetables.

Potassium AI Summary, Ages 19 Through 50 Years

AI for Men	
19–30 years	**4.7 g (120 mmol)/day of potassium**
31–50 years	**4.7 g (120 mmol)/day of potassium**
AI for Women	
19–30 years	**4.7 g (120 mmol)/day of potassium**
31–50 years	**4.7 g (120 mmol)/day of potassium**

Older Adults and the Elderly Ages 50+ Years

Evidence Considered in Setting the AI

Few humans studies are available that examine the effects of aging on renal and extrarenal adaptation to high potassium loads or dietary potassium deprivation. However, in two studies age-related decreases in both total body potassium and total exchangeable potassium, found in both men and women, were more evident in women (Davis et al., 1989; Rowe et al., 1992). Decreases in total body potassium may be due in part to the decrease in muscle mass that occurs with age (Rowe et al., 1992). In turn, the decrease in muscle mass with age may be, in part, a result of an inadequate intake of dietary potassium and its accompanying base (Frassetto et al., 1997).

In potassium adaptation studies in rats, the kaliuretic response to intravenous infusion of potassium chloride and the rise in plasma potassium have been shown not to be influenced by age (Friedman and Friedman, 1957; Rowe et al., 1992). However, when potassium intake was high, the efficiency of kaliuretic response to intravenous potassium chloride was impaired in the aging rat; a significantly greater plasma potassium concentration also occurred (Friedman and Friedman, 1957; Rowe et al., 1992). Following bilateral nephrectomy, the rise in plasma potassium concentration was also higher in the aged rats that were on a high potassium, but not normal potassium, intake. The renal and extrarenal impairment in potassium adaptation was associated with significant decreases in renal and colon Na^+/K^+-ATPase activity (Friedman and Friedman, 1957; Rowe et al., 1992). The applicablity of these findings to humans is still unclear.

Over the past several years there has been substantial attention paid to extrarenal potassium disposal. Beta-adrenergic mechanisms have been found to be responsible for potassium disposal during potassium infusion in healthy individuals across the adult age range (aged 23 to 85 years) (Rosa et al., 1980; Rowe et al., 1992). No observed effects of age on the extrarenal potassium disposal or the effect of β-adrenergic blockade was found. The effects of insulin concentration, β-adrenergic blockage, and age on potassium homeostasis during hyperinsulinemia was evaluated in 16 younger (22 to 37 years of age) and 10 older (63 to 77 years of age) men (Minaker and Rowe, 1982; Rowe et al., 1992). Increasing steady-state concentrations of insulin were associated with dose-dependent declines in plasma potassium concentration during the first hour of

insulin infusion, but during the second hour of insulin infusion, plasma potassium concentration continued to decline at the lowest insulin doses but began to rise at the highest insulin dose levels. This finding suggests the presence of a regulatory mechanism that influences insulin-mediated alterations in plasma potassium. The effect was not influenced by β-adrenergic blockade or aging (Minaker and Rowe, 1982; Rowe et al., 1992). These studies suggest that during aging, hormonal regulation of extrarenal potassium homeostasis remains normal.

Summary. In summary, for children, the AI was extrapolated from the adult AI based on energy intake. Older adults consume less energy than younger adults; however, because of the increased risk of elevated blood pressure with aging, the potassium need may be greater, and is thus not adjusted down for older adults. Because of the lack of evidence to suggest that the requirement for potassium differs in apparently normal, healthy older adults and the elderly compared with that of younger individuals, the AI is set at the same level of intake as for young adults.

Still, the AI does not apply to individuals with medical conditions or who are taking drugs that impair potassium excretion because of the potential for serious adverse effects on the heart from hyperkalemia (see later section, "Special Considerations"). Older individuals more commonly have such conditions or take such drugs and hence are at greater risk of hyperkalemia.

Potassium AI Summary, Ages 51+ Years

AI for Men	
51–70 years	**4.7 g (120 mmol) /day of potassium**
> 70 years	**4.7 g (120 mmol)/day of potassium**
AI for Women	
51–70 years	**4.7 g (120 mmol)/day of potassium**
> 70 years	**4.7 g (120 mmol)/day of potassium**

Pregnancy

Evidence Considered in Setting the AI

Accretion. There is little information on body potassium stores during pregnancy. The few available estimates range from cumula-

tive gains of 3.9 to 12.5 g (100 to 320 mmol), of which about 7.8 g (200 mmol) is destined for the products of conception (Forsum et al., 1988; Hytten and Leitch, 1971; Lindheimer and Katz, 2000). The latter value comes from a review of the literature by Hytten and Leitch (1971), including one serial study that measured total exchangeable potassium (MacGillivray and Buchanan, 1958). Additionally, one report provided estimates of potassium accretion as measured by the 40K naturally present in human tissues (Godfrey and Wordsworth, 1970). The accumulation at birth was 12 g of potassium (307 mmol), while at 1 month of age the total estimated potassium had decreased to 7 g (179 mmol) (Godfrey and Wordsworth, 1970).

A subsequent study, however, suggests that body potassium stores decrease early in gestation and then increase to only 3.9 g (100 mmol) above those present prior to conception (Forsum et al., 1988). Hormonal changes may affect potassium balance and deposition (Ehrlich and Lindheimer, 1972; Lindheimer and Katz, 1985). It has also been noted that pregnant women develop bicarbonaturia at substantially lower plasma bicarbonate levels than do nonpregnant women (Lindheimer and Katz, 2000).

Serum and Plasma Potassium Concentrations. Plasma and serum concentrations of potassium decrease about 0.2 to 0.3 mmol/L, which may not indicate hypokalemia until values decrease by 0.5 mmol, or to below 3 mmol/L. The reason for the decrement in circulating potassium concentrations during gestation is obscure, but could relate to the mild physiologic alkalemia of gestation in which blood concentrations of hydrogen ions have been shown to decrease about 2 to 4 nmol/L (Lindheimer and Katz, 1985).

Urinary Potassium Excretion. Of further interest and in striking contrast to nonpregnant women, pregnant women are resistant to the kaliuresis provoked by a combination of exogenous mineralocorticoids and a high sodium diet (Ehrlich and Lindheimer, 1972). This ability to conserve potassium in the face of high concentrations of potent mineralocorticoids, such as aldosterone or desoxycorticosterone, and the delivery to the distal nephron of substantial quantities of sodium, may be due to the increased concentrations of progesterone, also characteristic of gestation—a view supported by some (Ehrlich and Lindheimer, 1972; Lindheimer et al., 1987; Mujais et al., 1993), but not others (Brown et al., 1986). Of importance, this resistance to the kaliuretic effects may benefit women with certain potassium-losing diseases, such as primary aldoster-

onism and Bartter's syndrome (August and Lindheimer, 1999; Lindheimer et al., 1987). On the other hand, if the kidneys of pregnant women resist kaliuretic stimuli, one might speculate that women with underlying disorders that impair their ability to excrete potassium may be jeopardized by gestation. In this respect, there have been isolated descriptions of abnormally high potassium concentrations in pregnant women with sickle cell anemia and normal serum creatinine concentrations (Lindheimer et al., 1987), and at least one instance where a woman believed to have renal tubular acidosis developed hyperkalemia when treated with a potassium sparing diuretic (Szwed and Clarke, 1982).

Blood Pressure. Intervention trials that tested the effects of potassium intake on blood pressure during pregnancy are lacking. In one observational study, maternal potassium intake was not associated with pregnancy-associated hypertension or pre-eclampsia (Morris CD et al., 2001). One observational study showed that maternal prenatal potassium intake was inversely related to the infant's diastolic blood pressure at 6 and 12 months of age (McGarvey et al., 1991).

Summary. Overall, potassium accretion during pregnancy is very small and there is an absence of data to suggest that the requirement for potassium is different during pregnancy. Therefore, the AI is set at 4.7 g (120 mmol)/day, the same as for nonpregnant women.

Potassium AI Summary, Pregnancy

AI for Pregnancy	
14–18 years	**4.7 g (120 mmol)/day of potassium**
19–30 years	**4.7 g (120 mmol)/day of potassium**
31–50 years	**4.7 g (120 mmol)/day of potassium**

Lactation

Evidence Considered in Setting the AI

The potassium content of human milk averages around 0.5 g/L (13 mmol/L) during the first 6 months of lactation (see Table 5-9). Average milk production during the first 6 months of lactation is ≈ 0.78 L/d. Thus approximately 0.4 g (10 mmol)/day of potassium is needed for lactation during this period (0.5 g/L × 0.78 L/day =

0.4 g/day). In the absence of information to the contrary, it is assumed that the efficiency of conversion of dietary potassium to milk produced is almost 100 percent. Therefore, the AI for potassium during lactation is set at 5.1 g (130 mmol)/day (4.7 g + 0.4 g/day).

Potassium AI Summary, Lactation

14–18 years	**5.1 g (130 mmol)/day of potassium**
19–30 years	**5.1 g (130 mmol)/day of potassium**
31–50 years	**5.1 g (130 mmol)/day of potassium**

Special Considerations

Very Low Carbohydrate, High Protein Diets

Low-grade metabolic acidosis occurs with very low carbohydrate, high protein diets consumed by some individuals to promote and maintain weight loss. These diets, which may be adequate in potassium due to the high protein content, are inadequate as a source of alkali, because fruits are often excluded in these diets.

Over a 6-month period in which the metabolic consequences of such a diet were investigated in 51 overweight or obese volunteers, weight loss occurred, but the concomitant and intended ketosis led to an ongoing low-grade, metabolic acidosis, as judged by decreases in serum bicarbonate of 2 to 3 mmol/L (still in the normal range), as well as a persistent increase in urinary excretion of calcium of approximately 80 mg/day (Westman et al., 2002).

In a 6-week study of the metabolic effects of a low carbohydrate/high protein diet ingested by 10 adult subjects, a doubling of urinary net acid excretion was attended by a 50 percent increase in urinary excretion of calcium, which was not compensated by a commensurate increase in fractional intestinal calcium absorption (Reddy et al., 2002). Failure of intestinal compensation has been consistently demonstrated for acidosis-induced urine calcium losses (Breslau et al., 1988; Lemann et al., 1966).

Urinary excretion of citrate and serum osteocalcin also concurrently decreased with the increase in urinary excretion of calcium (Reddy et al., 2002). It was concluded that the diet delivered a marked acid load to the kidney, increased the risk of stone formation, led to negative calcium balance, and may have increased bone loss. Those diets that concomitantly restrict the intake of fruits like oranges, bananas, and grapes also restrict the intake of bicarbonate precursors like citrate, a restriction which would amplify the

acidogenic effect of the intended ketosis due to the lack of carbohydrate. There are no published studies of the long-term metabolic effects of this kind of diet in any group of individuals.

Replacement of Diuretic-Induced Potassium Losses

Substantial numbers of individuals receive treatment with diuretic therapies for medical conditions, primarily high blood pressure, but also congestive heart failure and chronic kidney disease. Thiazide diuretics (e.g., hydrochlorothiazide and chlorthalidone) and loop diuretics (e.g., furosemide) increase urinary potassium excretion, which in some instances leads to overt hypokalemia—that is, a serum potassium concentration of 3.5 mmol/L or less. Accordingly, many individuals on diuretic therapy are given a potassium supplement. In a recently completed trial (Furberg et al., 2002), approximately 8 percent of individuals assigned to low-dose chlorthalidone (12.5 to 25 mg/day) required a potassium supplement. Because of diuretic-induced urinary potassium losses, it is plausible that individuals on diuretic therapy should have an AI greater than 4.7 g (120 mmol)/day. However, available evidence is insufficient to confirm the need for a higher AI in such individuals.

Predisposition to Hyperkalemia

Several relatively common clinical conditions can predispose individuals to hyperkalemia, even at levels of potassium intake that are below the AI. The most common of these conditions are chronic kidney disease, heart failure, and type 1 diabetes, each of which can impair renal excretion of potassium. Angiotensin converting enzyme (ACE) inhibitor drug therapy, which is a recommended therapy for each of these conditions, increases the risk of hyperkalemia (Schoolwerth et al., 2001).

The risk for hyperkalemia during ACE inhibitor therapy increases as kidney function declines. The conclusion from a case series of 33 hypertensive patients in which serum potassium levels were measured before and after ACE inhibitor therapy was that serum potassium levels rarely rose to greater than 5.0 mmol/dL unless the estimated glomerular filtration rate (GFR) was less than 40 mL/minute (Textor et al., 1982). In this study, patients consumed between 2.7 and 3.1 g (70 and 80 mmol)/day of potassium. Whether a higher dietary intake of potassium would precipitate hyperkalemia is uncertain. In a case-control study of 1,818 medical outpatients on ACE inhibitor therapy, severe hyperkalemia (defined as serum potassium

> 6.0 mmol/day) was uncommon in patients less than 70 years old with normal renal function (Reardon and Macpherson, 1998); however, data on dietary potassium intake was not collected in this study. Since the 95th percentile estimates of potassium intake for men and women in the United States range from 4.3 to 5.1 g and 2.9 to 3.7 g/day, respectively (Appendix Table D-5), it can be assumed that many of these outpatients had intakes below the AI of 4.7 g (120 mmol)/day.

In case reports additional factors appear to precipitate hyperkalemia in ACE inhibitor-treated patients. These factors include use of potassium supplements, potassium-sparing diuretics, nonsteroidal anti-inflammatory agents, cyclo-oxygenase-2 (COX-2) inhibitors, and heparin (see Box 5-1). Although most case reports relating hyperkalemia and ACE inhibitor treatment occurred in individuals with diabetes, chronic kidney disease, and/or heart failure, there have been a few case reports in other settings. Two cases of hyperkalemia in older men were reported to be due to the use of a potassium-containing salt substitute while taking ACE inhibitor therapy (Ray et al., 1999). One case report documented fatal hyperkalemia in a 77-year-old woman after addition of COX-2 inhibitor therapy to a medical regimen that included an ACE inhibitor and a diet that included a banana each day (Hay et al., 2002). Her serum creatinine had been 0.9 mg/dL, which in retrospect might reflect subtle evidence of chronic kidney disease (Hay et al., 2002). This case illustrates the difficulty of using serum creatinine levels to diagnose early chronic kidney disease. Among older individuals, women who are non-African American often have serum creatinine values that appear to be "normal" (0.9 to 1.2 mg/dL) despite an underlying reduction in kidney function (Culleton et al., 1999).

Overall, because of the concern for hyperkalemia and resultant arrhythmias that might be life-threatening, the proposed AI should not be applied to individuals with chronic kidney disease, heart failure, or type 1 diabetes, especially those who concomitantly use ACE inhibitor therapy. Among otherwise healthy individuals with hypertension on ACE inhibitor therapy, the AI should apply as long as renal function is unimpaired.

INTAKE OF POTASSIUM

Sources

Good sources of potassium, as well as bicarbonate precursors, are fruits and vegetables (see Table 5-10). Foods that contain relatively

BOX 5-1 Clinical Circumstances That May Result in Hyperkalemia

- Impaired renal excretion of potassium
  - Severe reduction in glomerular filtration rate
    - Chronic kidney disease
    - Subacute-reversible
      - Volume depletion
      - Pharmacological inhibition by angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)
  - Effective hypoaldosteronism
    - Reduced synthesis due to
      - Addison's disease
      - Heparin administration
    - Reduced secretion of aldosterone
      - Hyporeninemia
        - Diabetic nephropathy
        - Obstructive nephropathy
        - Nonsteroidal anti-inflammatory drugs (e.g., indomethacin)
        - Cyclo-oxygenase-2 inhibitors (COX-2, e.g., Vioxx, Celebrex)
      - Reduced activity of angiotensin-converting enzyme
    - Reduced renal tubular response to aldosterone
      - Aldosterone-receptor blockers (e.g., spironolactone)
      - Type 4 renal tubular acidosis
  - Pharmacological inhibitors of distal renal tubular Na^+-K^+ exchange (e.g., amilioride, triamterene)
- Impaired systemic cellular accumulation of potassium
  - Hypoinsulinemia (type 1 diabetes)
  - Metabolic acidosis
  - β-andrenergic blockers (e.g., propanolol)
  - α-andrenergic agonists (e.g., phenylephrine)
- Excessive cellular release of potassium
  - Rhabdomyolosis
  - Tumor lysis
  - Leukemia

Clinical conditions that commonly occur together and that amplify their hyperkalemic effects

- Hyporeninemia/hypoaldosteronism and diabetic nephropathy
- Chronic kidney disease with either ACE or ARB therapy

SOURCE: Fisch et al. (1966); Gennari and Segal (2002); Kamel et al. (1996); Oster et al. (1995); Schoolwerth et al. (2001); Tannen (1986); Textor et al. (1982).

TABLE 5-10 Comparative Amounts of Approximate Potassium Content in Various Food Groups

Food Group	Potassium mg (mmol)/ 100 kcal	Examples
Leafy greens	1,500 (38)	Spinach, lettuce, romaine, cabbage, kale
Fruit of vine-based plants	1,200 (30)	Tomatoes, cucumbers, zucchini, eggplant, pumpkin
Root vegetables	975 (25)	Carrots, radishes, turnips, rutabaga, onions
Beans and peas	500 (13)	Kidney beans, peas, green beans, chick peas, soybeans
Tree fruits	430 (11)	Apples, oranges, bananas, apricots, grapes, strawberries
Tubers	400 (10)	Potatoes, sweet potatoes, yams
Milk and yogurt	350 (9)	Skimmed milk, whole milk, yogurt
Meats	230 (6)	Beef, lamb, pork, poultry, fish, rabbit
Nuts	110 (3)	Walnuts, cashews, almonds, brazil, hazelnuts
Eggs	90 (2.3)	Chicken eggs
Cereal grains	90 (2.3)	Wheat, rice, oats, rye
Cheese	150 (1.1)	Edam, stilton, cottage, cheddar

high amounts of potassium include spinach (≈ 840 mg [22 mmol] per cup), cantaloupe (315 mg [8 mmol] per 1/6 large), dry roasted almonds (210 [5 mmol] per oz.), brussels sprouts (250 mg [6 mmol] per 1/2 cup), mushrooms (550 mg [14 mmol] per 1 cup), bananas (470 mg [12 mmol] per 1 medium), oranges (200 mg [5 mmol] per 1 small), grapefruit (230 mg [6 mmol] per 1/2 large), and potatoes (600 mg [15 mmol] per potato without skin). The Adequate Intake (AI) for adults of 4.7 g (120 mmol)/day of potassium can be achieved by consuming a diet that contains generous amounts of potassium-rich fruits and vegetables.

While meat, milk, and cereal products contain potassium, their content of bicarbonate precursors does not sufficiently balance the amount of acid-forming precursors, such as sulfur amino acids, found in higher protein foods (Lemann et al., 2003). Tables of citrate and bicarbonate content of foods are lacking, making it difficult to estimate the amount consumed of these other food components.

On a calorie basis, the comparative amounts of potassium in various food groups, expressed in mg/100 kcal, are shown in Table 5-10. As for many other nutrients, from a nutrient density perspec-

tive, the richest sources of potassium are leafy green vegetables, fruit from vines, and root vegetables.

Salt substitutes currently available in the marketplace range from 440 mg to 2,800 mg (11 to 72 mmol)/tsp of potassium, all as potassium chloride (Pennington, 1998; Riccardella and Dwyer, 1985). In the Third National Health and Nutrition Examination Survey (NHANES III), less than 10 percent of respondents reported that they used a reduced-sodium salt or a salt substitute (Loria et al., 2001). The maximum amount of potassium in over-the-counter supplements is 0.099 g (2.5 mmol) (Medical Economics, 2001).

Table 5-11 provides an estimate of the potassium intake from foods when consuming approximately 2,200 kcal/day, the combined average energy intake of young men and women (IOM, 2002), while meeting recommended intakes for other nutrients. This table illustrates that potassium intake at levels in the range of the AI (4.7 g/day or 120 mmol/day) can be achieved by consuming a diet rich in fruits and vegetables.

Intake

Based on intake data from the NHANES III (Appendix Table D-5), the median intake of potassium in the United States ranged from 2.8 to 3.3 g (72 to 84 mmol)/day for men and 2.2 to 2.4 g (56 to 61 mmol)/day for women. The median potassium intakes of white respondents exceeded that of African-American respondents. The median intakes of potassium by adults obtained from Canadian surveys conducted between 1990 and 1999 in 10 provinces ranged from 3.2 to 3.4 g (82 to 87 mmol)/day for men and 2.4 to 2.6 g (62 to 67 mmol)/day for women (Appendix Table F-2), indicating that on average, Canadian intake of potassium was somewhat greater than that of adults in the United States. The percentage of men and women who consumed equal to or greater than the AI was less than 10 and 1 percent, respectively, in the United States.

These dietary intake surveys do not include estimates of the usage of salt substitutes. Less than 10 percent of those surveyed in NHANES III reported using salt substitutes or a reduced-sodium salt (Loria et al., 2001). No other data were found that estimate the intake of potassium from various salt substitutes on the market.

While there are very few data regarding potassium intake during pregnancy, the Calcium for Prevention of Preeclampsia trial (CPEP) estimated intake using dietary recalls in 4,589 participants at recruitment, during weeks 13 to 20 of gestation (Morris CD et al., 2001). Daily potassium intake of the 3,125 women who remained

TABLE 5-11 Daily Potassium Intake from a Diet Providing 2,200 kcal

Meal	Food/Beverage Consumed	Calories (kcal)	Potassium (mg)
Breakfast	Shredded wheat miniatures (1 cup)	183	248
	Cantaloupe, cubed (½ cup)	27	214
	Milk, 1% (8 oz)	102	290
	Orange juice (6 oz)	82	355
	White toast (1 slice) with unsalted margarine vegetable oil spread (1 tsp)	89	30
	Coffee, black, unsweetened (12 oz)	13	171
	Total for meal	**496**	**1,278**
Snack	Banana (1 medium)	105	422
	Water (1 cup)	0	0
	Total for meal	**105**	**422**
Lunch	Sandwich with turkey (2 oz), swiss cheese (1 oz), lettuce (2 leaves), tomato (¼″ slice), mayonnaise (1 tbsp) and whole wheat bread (2 slices)	395	499
	Baby carrots (8)	28	190
	Fig bar cookies (2)	111	66
	Iced tea, brewed, decaffeinated (16 oz)	5	176
	Total for meal	**539**	**857**
Snack	Almonds, dry roasted, unsalted (¼ cup)	206	257
	Raisins (¼ cup)	108	272
	Milk, 1% (8 oz)	102	290
	Water (12 oz)	0	0
	Total for Meal	**416**	**819**
Dinner	Baked salmon (3 oz)	151	257
	Long-grain brown rice (½ cup cooked)	108	42
	Tossed salad (1½ cups) with safflower oil and vinegar dressing (2 tbsp)	155	371
	Asparagus (6 spears)	20	202
	Wheat roll, (1 medium) with unsalted margarine vegetable oil spread (1 tsp)	101	34
	Angel food cake (1 slice) with sliced strawberries (½ cup) and whipped cream topping (2 tbsp)	114	162
	Iced tea, brewed, decaffeinated (16 oz)	5	176
	Coffee, black, unsweetened, decaffeinated (8 oz)	9	114
	Total for meal	**663**	**1,492**

TABLE 5-11 Continued

Meal	Food/Beverage Consumed	Calories (kcal)	Potassium (mg)
	Daily total	**2,219 kcal**	**4,868 mg** (124 mmol)

NOTE: This diet meets the Adequate Intake or Recommended Dietary Allowance for adult men and women for all nutrients for which one has been established (for fiber, it meets the ratio of 14 g/1,000 kcal) and provides energy nutrients within the acceptable macronutrient distribution ranges. Nutrient totals may not equal the sum of the parts due to rounding. Vegetables and rice were prepared without salt.

FOOD COMPOSITION DATA: U.S. Department of Agriculture Agricultural Research Service, Nutrient Database for Standard Reference, Release 16.

DATA SOURCE: Environ International.

nonhypertensive throughout pregnancy averaged 3.1 g (79 mmol)/day. While this population group had over-representation by African-American and Hispanic pregnant women, in two other studies in which potassium excretion was measured serially throughout gestation, 24-hour urinary excretion averaged 2.0 to 2.3 g (50 to 60 mmol)/day of potassium (Brown and et al., 1986; Wilson et al., 1980). While there were few (n = 83) pregnant women in NHANES III, and even fewer (n = 19) lactating women (Appendix Table D-6), their intake of potassium intake was substantially greater than their nonpregnant counterparts, with median intakes of 2.8 g (72 mmol)/day and 3.8 g (97 mmol)/day, respectively.

ADVERSE EFFECTS OF OVERCONSUMPTION

Hazard Identification

Gastrointestinal Discomfort

Gastrointestinal discomfort has been reported with some forms of potassium supplements, but not with potassium from diet. When healthy individuals were provided 2.3 g (60 mmol)/day of potassium chloride for 18 days in the form of a wax/polymer matrix tablet, a powder-in-liquid formulation, or a microencapsulated gelatin capsule, there was a significant increase in gastrointestinal distress reported for the wax/polymer matrix as compared with the other two (Sinar et al., 1986). Gastrointestinal discomfort was also

reported by some patients receiving 0.8 to 1.6 g (20 to 40 mmol)/day of potassium chloride either as a wax-matrix tablet (5 of the 17 receiving the treatment) or as a microencapsulated tablet (6 of the 17) (Pietro and Davidson, 1990).

Ulceration of gastrointestinal tract mucosa and perforation of the small bowel have been reported in patients using various potassium chloride supplements (Lambert and Newman, 1980; Leijonmarck and Raf, 1985). In a placebo-controlled trial that provided 2.3 g (60 mmol)/day of microencapsulated potassium to 175 prehypertensive subjects for 6 months, high pill compliance but no serious gastrointestinal effect was reported (Whelton et al., 1995). Overall, the specific product/vehicle appears to be a critical determinant of the risk of gastrointestinal side effects from supplemental potassium.

Arrhythmia from Hyperkalemia

Cardiac arrhythmias from hyperkalemia are the most serious consequence of excessive potassium intake. The typical sequence of findings is hyperkalemia, followed by conduction abnormalities on electrocardiogram (ECG) and then cardiac arrhythmias, which can be life-threatening. Such consequences result from either a high plasma concentration of potassium or from rapid and extreme changes in its concentration (Kallen et al., 1976). At typical dietary intakes of potassium, the normal range of plasma concentration of potassium is 3.5 to 5.0 mmol/L. The actual level at which hyperkalemia increases the risk of serious arrhythmias is uncertain, but is likely at a level greater than 5.5 mmol/L.

Acute toxicity from accidental or intentional consumption of large quantities of potassium chloride or potassium-containing salt substitutes by apparently healthy individuals has been reported (Kallen et al., 1976; Su et al., 2001; Wetli and Davis, 1978). However, such evidence of acute toxicity is of limited value in assessing the potential hazards from chronic ingestion of high levels of potassium. In clinical trials that assessed the effects of potassium supplementation as high as 15.6 g (400 mmol)/day over a period of at least 5 days in apparently healthy individuals, plasma levels of potassium increased but remained within the normal range (see Table 5-12). Importantly, there were no instances of hyperkalemia reported in these studies.

However, in individuals whose urinary potassium excretion is impaired by a medical condition, drug therapy, or both, instances of life-threatening hyperkalemia have been reported. There have been several case reports of hyperkalemia in individuals who reported

use of a potassium-containing salt substitute while under treatment for chronic diseases (Haddad and Strong, 1975; Ray et al., 1999; Snyder et al., 1975) (see Table 5-13). These individuals had some type of heart or renal disease and therefore were taking other medications, including ACE inhibitors. The potassium-containing salt substitute might have been prescribed to reduce sodium chloride intake, to replace diuretic-induced potassium losses, or both. Such patients are at risk both for hypokalemia and hyperkalemia and therefore require close medical supervision.

Dose-Response Assessment

In otherwise healthy individuals (that is, individuals without impaired urinary potassium excretion from a medical condition or drug therapy), there have been no reports of hyperkalemia resulting from acute or chronic ingestion of potassium naturally occurring in food. Hyperkalemia might theoretically occur if the capacity of the normal kidney to excrete a potassium load is exceeded. The maximum excretion rate of normal kidneys after adaptation to high levels of intake has been estimated to be approximately 31.3 g (800 mmol)/day for adults (Berliner, 1961), a level that would be difficult to achieve from food alone. Gastrointestinal discomfort has been reported with some forms of potassium supplements, but not with potassium from foods.

UL Summary

Adults. In otherwise healthy individuals (i.e., individuals without impaired urinary potassium excretion from a medical condition or drug therapy), there is no evidence that a high level of potassium from foods has adverse effects. Therefore, a Tolerable Upper Intake Level (UL) for potassium from foods is not set for healthy adults.

In contrast, supplemental potassium can lead to acute toxicity in healthy individuals. Also, chronic consumption of a high level of potassium can lead to hyperkalemia in individuals with impaired urinary potassium excretion (see later section, "Special Considerations"). Hence, supplemental potassium should only be provided under medical supervision because of the well-documented potential for toxicity.

Infants and Children. Almost all of the potassium that appears in urine is secreted by the last half of the distal tubule (Schultze, 1973).

TABLE 5-12 Effects of Chronic Intake of High Levels of Potassium

Reference	Study Design	Diet
Nonhypertensive individuals		
Hene et al., 1986	6 men, 24 ± 2 yr 2-wk crossover	Control diet: 3.1 g (80 mmol) potassium (K), 3.4 g (150 mmol) sodium (Na) High-K diet: 8.6 g (220 mmol) K, 3.4 g (150 mmol) Na (additional potassium as K citrate)
Witzgall and Behr, 1986	16 men, 27 ± 6 yr, control diet 2 wk prior to loading	Control diet: 2.3 g (60 mmol) K, 4.6 g (200 mmol) Na High K diet: control diet + 7.8 g (200 mmol) as K citrate and K hydrogen carbonate = 10.1 g (260 mmol) K total
Rabelink et al., 1990	3 men, 3 women, 22–26 yr	5-d control diet: 3.9 g (100 mmol) K, 2.3 g (100 mmol) Na 20-d high K diet: 15.6 g (400 mmol)K, 2.3 g (100 mmol) Na
Deriaz et al., 1991	8 men, 26 ± 2 yr 5-d crossover	Baseline diet: 2.7 g (69 mmol) K High K diet: 6.4 g (163 mmol) K
Dluhy et al., 1972	8 women, 2 men Crossover	5 subjects: 0.23 g (10 mmol) Na 1.6 g (40 mmol) K, 6–7 d 7.8 g (200 mmol) K, 3 d 5 subjects: 4.6 g (200 mmol) Na 1.6 g (40 mmol) K, 6–7 d 7.8 g (200 mmol) K, 3 d
Zoccali et al., 1985	10 men, 20–29 yr 5-d crossover	Baseline diet: 3.0 g (76 mmol) K, 3.4 g (145 mmol) Na High K diet: 6.9 g (176 mmol) K, 3.4 g (145 mmol) Na
Hypertensive individuals		
Zoccali et al., 1985	10 men, 9 women, 26–53 yr 2-wk crossover	Baseline diet: Normal diet + placebo Higher K diet: + 3.9 g (100 mmol) K

[a] SBP = systolic blood pressure, DBP = diastolic blood pressure.

Urinary Potassium (mmol/24 h)	Effects[a]
50 ± 12 233 ± 45	Serum K within normal limits but 10% higher ($p < 0.05$) with K load
≈ 60	↑ Plasma K ($p < 0.01$) (from 4.3 to 4.6 mmol/L) ↓ SBP ($p < 0.01$); ↓ DBP ($p < 0.01$)
≈ 220	↑ Plasma renin in 13 of 16 subjects; no adverse effects identified
82 385	With high K diet, ↑ plasma K ($p < 0.05$); plasma renin and aldosterone, while increased significantly ($p < 0.01$) after 2 d, were back to baseline levels by 20 d
50 119	Serum K was within normal limits
	Fasting plasma aldosterone levels ↑ with increased K regardless of Na intake; no other effects noted
59 161	Serum K was 10% higher ($p < 0.05$) on high K diet, but still within normal range No other changes noted
58 139	4 patients withdrew from the study: 1 due to diarrhea from the K supplement; 1 due to ↑ BP when receiving placebo; 2 due to taste of K supplement

TABLE 5-13 Studies and Case Reports of Adverse Effects Due to Chronic Intake of High Levels of Potassium

Case Report	Description of Patient
Haddad and Strong, 1975	39-yr-old woman, Lupus Erythematosus, w/chronic renal failure (creatinine clearance = 30 mL/min)
Snyder et al., 1975	75-yr-old woman, history of myocardial infarction, on a low sodium diet
Ray et al., 1999	67-yr-old man; hypertensive, previous coronary artery bypass surgery and left ventricular dysfunction
Ray et al., 1999	64-yr-old man; 24-yr history of diabetes mellitus and recent systolic hypertension, retinopathy, and renal impairment; on a low sodium diet

While an infant's renal secreting capacity is initially less than adults, renal function rapidly reaches the normal adult level in early childhood, so little concern exists for consumption of high levels of potassium from foods. Because the renal secreting ability of normal infants is not fully developed, potassium intake should be limited to that contained in formula and complementary foods.

Pregnancy. Other than occasional gastrointestinal discomfort as noted above from the use of certain forms of supplemental potassium, adverse effects from high intakes of potassium have not been noted in apparently healthy individuals, which would include pregnant women who are not identified as having hypertension or preeclampsia. Therefore, a UL for potassium is not set for healthy women during normal pregnancy.

Lactation. As with other adults, there is little reason to restrict the potassium intake of healthy lactating women due solely to lac-

Potassium Amount Ingested	Adverse Effect	Medications
Ad lib use of salt substitute	Serum potassium = 7.4 mmol/L	Spironolactone, a potassium-sparing diuretic
Ad lib use of a "lite" salt substitute	Edema, shortness of breath, right-sided and left-sided congestive heart failure	None reported
Estimate of 2.7 g (70 mmol)/d of potassium as "LoSalt" for previous week; diet high in fruits and vegetables	Serum potassium = 7.6 mmol/L; loss of consciousness, dizziness, intermittent vomiting	Atenolol, furosemide, aspirin, and lisinopril (an angiotensin converting enzyme inhibitor)
Estimate of 5.2 g (133 mmol)/d of potassium as "Lo Salt" previously; diet estimated to also provide 2.7 g (70 mmol)/d	Serum potassium = 7 mmol/L	Enalapril (an angiotensin converting enzyme inhibitor)

tation. Therefore, a UL is not set for healthy women during this period.

Special Considerations

Problem Pregnancy. It is suggested that high potassium levels be consumed with care in women with problem pregnancies, such as preeclampsia. High concentrations of the antikaliuretic hormone progesterone (which circulate during gestation) may make women with undetected renal dysfunction or with a sudden decrease in glomerular filtration rate (as occurs with preeclampsia) more likely to develop hyperkalemia when potassium intake is high.

Other Situations. Clinical settings in which high intakes of potassium could pose a serious risk include type 1 diabetes, chronic renal insufficiency (e.g., GFR < 40 mL/minute), end-stage renal disease, severe heart failure, and adrenal insufficiency (see Box 5-1). In these

situations, medical supervision is typically provided, including individualized diet instruction (IOM, 2000), and a potassium intake below the AI is often appropriate. For individuals with these diseases or clinical conditions, salt substitutes (containing potassium chloride) should be used cautiously. While adverse events following high potassium consumption usually do not occur in these special populations, there are case studies cited in the literature indicating that these groups are vulnerable (see Table 5-13).

RESEARCH RECOMMENDATIONS

- Dose-response trials testing the effects of different levels of potassium intake on blood pressure at different levels of sodium intake.
- Additional dose-response trials evaluating the effect of potassium on salt sensitivity in subgroups of the population that are salt sensitive (e.g., African Americans, older persons, and persons with hypertension, chronic kidney disease, or diabetes).
- Randomized clinical trials to compare the effect of different potassium salts on blood pressure and other outcomes at different levels of sodium intake.
- Development of improved measurements and instruments that assess total potassium intake and total body potassium.
- Trials that test the efficacy of increased potassium intake on preventing stroke.
- Trials that test the main and interactive effects of potassium and sodium intake on bone mineral density and, if feasible, bone fractures.
- Trials testing the main and interactive effects of sodium and potassium intake on the risk of kidney stones.
- Studies to assess the main and interactive effects of potassium and sodium intake on glucose intolerance and insulin resistance.
- Studies on the role of potassium intake during infancy and childhood on blood pressure later in life.
- Potassium balance studies during pregnancy.
- Better estimates of potassium losses in sweat with various dietary, activity, and environmental conditions in diverse populations.
- Development of food tables for citrate and bicarbonate.
- Studies on the effects of chronic, low-grade metabolic acidosis on clinical outcomes, particularly kidney stones and osteoporosis.
- Trials to assess the effects of high potassium intake on serum potassium levels and blood pressure in the setting of early stages of renal insufficiency (with and without ACE inhibitor therapy).

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6
Sodium and Chloride

SUMMARY

The cation sodium and the anion chloride are normally found in most foods together as sodium chloride, also termed salt. For this reason, this report presents data on the requirements for and the effects of sodium and chloride together.[1]

Sodium and chloride are required to maintain extracellular volume and plamsa osmolality. Human populations have demonstrated the capacity to survive at extremes of sodium intake from less than 0.2 g (10 mmol)/day of sodium in the Yanomamo Indians of Brazil to over 10.3 g (450 mmol)/day in Northern Japan. The ability to survive at extremely low levels of sodium intake reflects the capacity of the normal human body to conserve sodium by markedly reducing losses of sodium in the urine and sweat. Under conditions of maximal adaptation and without sweating, the minimal amount of sodium required to replace losses is estimated to be no more than 0.18 g (8 mmol)/day. Still, it is unlikely that a diet providing this level of sodium intake is sufficient to meet dietary requirements for other nutrients.

[1] In view of the format of published data, this report presents intake data primarily as g (mmol)/day of sodium and of chloride, rather than g (mmol)/day of sodium chloride (salt). To convert mmol to mg of sodium, chloride, or of sodium chloride, multiply mmol by 23, 35.5, or 58.5 (the molecular weights of sodium, chloride, and sodium chloride), respectively.

Because of insufficient data from dose-response trials, an Estimated Average Requirement (EAR) could not be established, and thus a Recommended Dietary Allowance could not be derived. Hence, an Adequate Intake (AI) is provided.

The AI for sodium is set for young adults at 1.5 g (65 mmol)/day (3.8 g of sodium chloride) to ensure that the overall diet provides an adequate intake of other important nutrients and to cover sodium sweat losses in unacclimatized individuals who are exposed to high temperatures or who become physically active as recommended in other dietary reference intakes (DRI) reports. This AI does not apply to individuals who lose large volumes of sodium in sweat, such as competitive athletes and workers exposed to extreme heat stress (e.g., foundry workers and fire fighters). The AI for sodium for older adults and the elderly is somewhat less, based on lower energy intakes, and is set at 1.3 g (55 mmol)/day for men and women 50 through 70 years of age, and at 1.2 g (50 mmol)/day for those 71 years of age and older.

Concerns have been raised that a low level of sodium intake adversely affects blood lipids, insulin resistance, and cardiovascular disease risk. However, at the level of the AI, the preponderance of evidence does not support this contention. A potential indicator of an adverse effect of inadequate sodium is an increase in plasma renin activity. However, in contrast to the well-accepted benefits of blood pressure reduction, the clinical relevance of modest rises in plasma renin activity as a result of sodium reduction is uncertain.

The AI for chloride is set at a level equivalent on a molar basis to that of sodium, since almost all dietary chloride comes with the sodium added during processing or consumption of foods. Thus the AI for chloride for younger adults is 2.3 g (65 mmol)/day of chloride, which is equivalent to 3.8 g/day sodium chloride. The AIs for chloride for older adults and the elderly are 2.0 and 1.8 g of chloride per day respectively, equivalent to 3.2 g (55 mmol) and 2.9 g (50 mmol) of sodium chloride per day.

The major adverse effect of increased sodium chloride intake is elevated blood pressure, which has been shown to be an etiologically related risk factor for cardiovascular and renal diseases. On average, blood pressure rises progressively with increased sodium chloride intake. The dose-dependent rise in blood pressure appears to occur throughout the spectrum of sodium intake. However, the relationship is nonlinear in that the blood pressure response to changes in sodium intake is greater at sodium intakes below 2.3 g (100 mmol)/day than above this level. The strongest

dose-response evidence comes from those clinical trials that specifically examined the effects of at least three levels of sodium intake on blood pressure. The range of sodium intake in these studies varied from 0.23 g (10 mmol)/day to 34.5 g (1,500 mmol)/day. Several trials included sodium intake levels close to 1.5 g (65 mmol) and 2.3 g (100 mmol)/day.

While blood pressure, on average, rises with increased sodium intake, there is well-recognized heterogeneity in the blood pressure response to changes in sodium chloride intake. Individuals with hypertension, diabetes, and chronic kidney disease, as well as older-age persons and African Americans, tend to be more sensitive to the blood pressure-raising effects of sodium chloride intake than their counterparts.[2] Genetic factors also influence the blood pressure response to sodium chloride. There is considerable evidence that salt sensitivity is modifiable. The rise in blood pressure from increased sodium chloride intake is blunted in the setting of a diet that is high in potassium or that is low in fat, and rich in minerals; nonetheless, a dose-response relationship between sodium intake and blood pressure still persists. In nonhypertensive individuals, a reduced salt intake can decrease the risk of developing hypertension (typically defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥ 90 mm Hg).

The adverse effects of higher levels of sodium intake on blood pressure provide the scientific rationale for setting the Tolerable Upper Intake Level (UL). Because the relationship between sodium intake and blood pressure is progressive and continuous without an apparent threshold, it is difficult to precisely set a UL, especially because other environmental factors (weight, exercise, potassium intake, dietary pattern, and alcohol intake) and genetic factors also affect blood pressure. For adults, a UL of 2.3 g (100 mmol)/day is set. In dose-response trials, this level was commonly the next level above the AI that was tested. It should be noted that the UL is not a recommended intake and, as with other ULs, there is no benefit to consuming levels above the AI.

[2] In research studies, different techniques and quantitative criteria have been used to define salt sensitivity. In general terms, salt sensitivity is expressed as either the reduction in blood pressure in response to a lower salt intake or the rise in blood pressure in response to sodium loading. Salt sensitivity differs among subgroups of the population and among individuals within a subgroup. The term "salt sensitive blood pressure" applies to those individuals or subgroups who experience the greatest change in blood pressure from a given change in salt intake—that is, the greatest reduction in blood pressure when salt intake is reduced.

Among certain groups of individuals who are most sensitive to the blood pressure effects of increased sodium intake (e.g., older persons; African Americans; and individuals with hypertension, diabetes, or chronic kidney disease), their UL may well be lower. These groups also experience an especially high incidence of blood pressure-related cardiovascular disease. In contrast, for individuals who are unacclimatized to prolonged physical activity in a hot environment, their needs may exceed the UL because of sodium sweat losses.

It is well-recognized that the current intake of sodium for most individuals in the United States and Canada greatly exceeds both the AI and UL. Progress in achieving a reduced sodium intake will likely be incremental and will require changes in individual behavior towards salt consumption, replacement of high salt foods with lower salt versions, increased collaboration of the food industry with public health officials, and a broad spectrum of additional research. The latter includes research designed to develop reduced sodium food products while maintaining flavor, texture, consumer acceptability, and low cost.

BACKGROUND INFORMATION

Function

Sodium is the principal cation of the extracellular fluid and functions as the osmotic determinant in regulating extracellular fluid volume and thus plasma volume. Approximately 95 percent of the total sodium content of the body is found in extracellular fluid. Sodium is also an important determinant of the membrane potential of cells and the active transport of molecules across cell membranes. The concentration of sodium within the cell is typically less than 10 percent of that outside cell membranes, and an active, energy-dependent process is required to maintain this concentration gradient. Chloride, in association with sodium (i.e., sodium chloride), is the principal osmotically active anion in the extracellular fluid and is also important in maintaining fluid and electrolyte balance; it also serves as an important component of gastric juice as hydrochloric acid.

Physiology of Absorption and Metabolism

Sodium and chloride ions are typically consumed as sodium chloride. Absorption of sodium and chloride occurs primarily in the

small intestine and is approximately 98 percent across a wide intake range. The majority of ingested sodium chloride is excreted in the urine, provided that sweating is not excessive (Holbrook et al., 1984; Pitts, 1974). In humans who are at "steady-state" conditions of sodium and fluid balance and who have minimal sweat losses, the amount of sodium excreted in urine roughly equals intake. This phenomenon occurs due to the capacity of the normal human kidney to filter some 25,000 mmol of sodium each day and to reabsorb, by extremely precise mechanisms, 99 percent or more of the filtered load (Valtin and Schafer, 1995). Absorbed sodium and chloride remain in the extracellular compartments, which include plasma (at concentrations of 140 mmol/L for sodium and 104 mmol/L for chloride), interstitial fluid (at concentrations of 145 mmol/L for sodium and 115 mmol/L for chloride), and plasma water (at concentrations of 150 mmol/L for sodium and 111 mmol/L for chloride); intracellular concentrations in tissues such as muscle are 3 mmol/L for sodium and 3 mmol/L for chloride (Oh and Uribarri, 1999). Sodium is maintained outside of the cell via the Na^+/K^+-ATPase pump.

There are various systems and hormones that influence sodium and chloride balance, including the renin-angiotensin-aldosterone axis, the sympathetic nervous system, atrial natriuretic peptide, the kallikrein-kinin system, various intrarenal mechanisms, and other factors that regulate renal and medullary blood flow. Angiotensin II, a potent vasoconstrictor, regulates the proximal tubule of the nephron to promote sodium and chloride retention and also to stimulate the release of aldosterone from the adrenal cortex (Valtin and Schafer, 1995). Aldosterone promotes the renal reabsorption of sodium in the distal tubule of the nephron by mineralocorticoid receptor-mediated exchange for hydrogen and potassium ions. With reduced salt intake, reduced blood volume, or reduced blood pressure, the renin-angiotensin-aldosterone axis is stimulated. When the renin-angiotensin-aldosterone system is less responsive, as with advancing age, there is a greater blood pressure reduction from a reduced intake of sodium chloride (Cappuccio et al., 1985; Weinberger et al., 1993a).

Atrial natriuretic peptide (ANP) is released in response to elevated blood volume and serves as a counter-regulatory system to the renin-angiotensin-aldosterone system. ANP decreases the release of renin and therefore the release of angiotensin II and aldosterone and increases the glomerular filtration rate. These actions contribute to reductions in blood volume and blood pressure.

The sympathetic nervous system is another major regulatory sys-

tem for sodium and chloride excretion through at least three mechanisms: alteration in renal medullary blood flow, release of renin, and direct effects on the renal tubules. Similar to the renin-angiotensin-aldosterone system, the sympathetic nervous system is activated during sodium depletion and suppressed during sodium excess (Luft et al., 1979a). With increased extracellular fluid volume, there is increased blood flow in the medulla (the inner part of the kidney), resulting in a decreased sodium concentration of the fluid delivered to the ascending limb of Henle's loop in the renal tubule. This decrease leads to reduced sodium reabsorption of the kidney's nephron so that more sodium is delivered to the distal tubules for excretion.

Intrarenal mechanisms are also important for sodium and chloride homeostasis. These mechanisms include locally released prostaglandins, kinins, angiotensin, endothelial relaxing factor, and other less-well defined factors.

Other Forms of Sodium

Sodium is consumed as sodium chloride (salt), sodium bicarbonate, and as sodium in a variety of forms provided in processed foods (e.g., monosodium glutamate and other food additives, such as sodium phosphate, sodium carbonate, and sodium benzoate). Still, the major form of dietary sodium is sodium chloride (Fregly, 1984; Mattes and Donnelly, 1991), which accounts for approximately 90 percent of the total sodium intake in the United States.

Sodium bicarbonate is used as an ingredient in foods. It can also be used in the treatment of metabolic acidosis because its bicarbonate component induces an increase in plasma bicarbonate concentration, the prime "metabolic" determinant of blood pH (the numerator of the Henderson-Hasselbalch equation[3]), with the pCO_2 concentration being determined by respiration. Normally bicarbonate is the major determinant of plasma alkalinity. Although there is strong evidence that metabolic acidosis, which occurs in chronic renal insufficiency, is an important determinant of deleterious muscle and bone catabolism (Bushinsky, 1998; Mitch, 1998), sodium bicarbonate is not widely used clinically to correct such acido-

[3] $pH = pK_1 + \log \frac{[BA]}{[HA]}$, where BA is the ionized salt of the acid HA; in the case of the bicarbonate-carbonic acid buffer system in blood, the $pK_1 = 6.1$, and the concentration of carbonic acid [H_2CO_3] is based on the blood concentration of pCO_2.

sis. This is because large volumes of sodium bicarbonate are required, leading to concern that the sodium load may induce plasma volume overload.

It might be expected that sodium chloride loading rather than sodium bicarbonate loading would substantially expand plasma volume because sodium and chloride are both distributed as osmotic agents almost restrictively within the plasma-containing extracellular fluid. In contrast, bicarbonate is distributed throughout the much larger total body water. However, in a variety of clinical circumstances, sodium bicarbonate and/or sodium citrate appear to induce an expansion of plasma volume, as judged by suppression of plasma renin activity and the plasma concentration of aldosterone (Kurtz et al., 1987; Luft et al., 1990; Schorr et al., 1996; Sharma et al., 1992) and by changes in insulin space (Van Goidsenhoven et al., 1954). Yet, in these studies, sodium loading without chloride (e.g., with sodium bicarbonate) did not raise blood pressure to the same extent as sodium chloride (Luft et al., 1990; Schorr et al., 1996).

INDICATORS CONSIDERED FOR ESTIMATING THE REQUIREMENTS FOR SODIUM AND CHLORIDE

The following section reviews the potential markers for adverse effects resulting from insufficient sodium intake in apparently healthy individuals.

Sodium Balance

When substantial sweating does not occur, total obligatory sodium losses are very small, up to 0.18 g/day or 8 mmol/day (Table 6-1) (Dahl, 1958). For this reason, in a temperate climate or even a

TABLE 6-1 Obligatory Losses of Sodium

	g/d	mmol/d
Urine	0.005–0.035	0.2–1.5
Skin (nonsweating)	0.025	1.1
Feces	0.010–0.125	0.4–5.4
Total	0.040–0.185	1.7–8.0

SOURCE: Dahl (1958).

tropical climate, acclimatized persons can survive on extremely low sodium intakes (Kempner, 1948; Oliver et al., 1975).

Urine and Feces

In nonsweating individuals living in a temperate climate who are in a steady-state of sodium and fluid balance, urinary sodium excretion is approximately equal to sodium intake (i.e., 90 to 95 percent of total intake is excreted in urine) (Holbrook et al., 1984; Pietinen, 1982). Obligatory urinary losses of sodium in adults are approximately 23 mg (1 mmol)/day (Dole et al., 1950). This estimated level of excretion is similar to those that have been actually measured in studies of the Yanomamo Indians in Brazil: in one study sodium excretion of 26 men averaged 23.5 ± 34.7 mg (1.02 ±1.51 mmol)/day (Oliver et al., 1975), and in a subsequent study (n = 195), urinary sodium excretion was 20.7 ± 52.9 mg (0.9 ± 2.3 mmol)/day (Rose et al., 1988).

Excretion of sodium in the stool is minimal. When sodium intakes ranged from 0.05 to 4.1 g/day of sodium, only about 0.01 to 0.125 g (0.4 to 5.4 mmol)/day appeared in the stool (Dahl, 1958; Dole et al., 1950; Henneman and Dempsey, 1956). In a sodium balance study with three levels of intake, 1.5, 4.0, and 8.0 g (66, 174, and 348 mmol)/day (Allsopp et al., 1998), fecal sodium excretion increased as sodium intake rose. Still, fecal excretion of sodium was less than 5 percent of intake even at the highest level of sodium intake (Table 6-2).

Skin and Sweat

Daily dermal losses of sodium have been reported to average less than 0.025 g (1.1 mmol)/day (Dahl, 1958; Dahl et al., 1955). In another study, estimated obligatory dermal losses of sodium ranged from 0.046 to 0.09 g (2 to 4 mmol)/day (Fregly, 1984). Sweat sodium loss depends on a number of factors, including: (1) the sweat rate, (2) sodium intake, and (3) heat acclimation (Allsopp et al., 1998). For these reasons, the sodium concentration in sweat varies widely. Most studies that measure sodium content of sweat are short-term (Table 6-3), and report sweat sodium concentrations rather than total sodium lost in sweat. Of note, in these studies intake data on dietary sodium was frequently not given. However, in the three studies where dietary sodium information was provided, dietary intakes were high (up to 8.7 g [378 mmol]/day).

TABLE 6-2 Sodium Balance at Three Levels of Sodium Intake

Sodium Intake (g/d)	Sodium Intake (mmol/d)	Number of Men	24-h Urinary Sodium, g (mmol)	24-h Fecal Sodium, g (mmol)	12-h Sweat Sodium, g (mmol)	Sodium Balance, g (mmol)
1.5	66	9	0.7 (32.4)	0.03 (1.4)	0.57 (24.8)	+0.005 (0.2)
4.0	174	9	2.1 (92.3)	0.12 (5.4)	0.89 (39.1)	+0.67 (29.1)
8.0	348	7	5.8 (251.3)	0.33 (14.2)	1.2 (52.6)	+0.34 (14.7)

NOTE: Reported values were obtained after 8 d on the assigned sodium level. Measurements were obtained at the end of the 8-d period of which the last 5 d were spent in an environmental chamber (40°C [104°F] from 8 am to 6 pm, and from 6 pm to 8 am at 25°C [77°F]).

SOURCE: Allsopp et al. (1998).

One study provided detailed information on sweat losses at three levels of dietary sodium intake (Allsopp et al., 1998). Men were exposed to heat in an environmental chamber at 40°C (104°F) for 10 hours/day of the last 5 days of an 8-day experimental period. Sweat sodium loss, as well as fecal and urinary sodium losses, were progressively greater across the three levels of sodium studied (1.5 g [66 mmol], 4 g [174 mmol], or 8 g [348 mmol]/day) (see Table 6-2). By the eighth day, participants on the lowest sodium level were in sodium balance. Plasma aldosterone concentrations were significantly increased during the low sodium condition and significantly decreased during the high sodium condition. Earlier studies, including a 10-day pre-post study, reported similar reductions in sodium sweat loss following exercise in the heat over time (Kirby and Convertino, 1986), as well as decreased sweat sodium concentration with heat acclimation without exercise (Allan and Wilson, 1971).

This reduction in sweat sodium concentration is a protective mechanism to minimize plasma volume loss. Conn (1949) demonstrated that healthy persons sweating 5 to 9 L/day could maintain sodium chloride balance on intakes ranging from as low as 1.9 g (83 mmol)/day to 3.2 g (139 mmol)/day of sodium chloride, the maximum intake provided.

In aggregate, available data indicate that healthy, free-living individuals can achieve sodium balance following acclimation under a variety of conditions, including low sodium intake and extreme heat.

TABLE 6-3 Sweat Sodium Concentration

Reference	Study Design
Adults	
Consolazio et al., 1963	3 men 37.8°C (100°F) 8.7 g/d sodium (378 mmol/d), 16 d
Murakami and Hirayama, 1964	16 Japanese adults Ambient temperature No dietary information
Allan and Wilson, 1971	3 subjects Unacclimated and acclimated, 40°C (104°F) for 1 h/d No diet information, 3 wk
Kirby and Convertino, 1986	10 men 1–2 h postexercise, 40°C (104°F), measured at 1 and 10 d of heat acclimation 3.2–3.5 g/d (141–152 mmol/d) sodium
Barr et al., 1991	6 subjects Moderate exercise for 6 h, 30°C (86°F); provided water or saline at 5.8 g/L (25 mmol/L) No dietary information
Meyer et al., 1992	16 men and women 42°C (107.6°F) and 40 min cycling No dietary information, 1 d
Allsopp et al., 1998	25 men, each on different dietary levels 25°C (77°F) for 3 d, acclimated at 40°C (104°F) for 5 d, 3 levels of sodium intake/d 1.5 g (66 mmol) (9 men) 4.0 g (174 mmol) (9 men) 8.0 g (348 mmol) (7 men), 8 d
Inoue et al., 1999	5 men Exercise 90 min/d, 43°C (109.4°F) No dietary information, 8 d
Children	
Murakmi and Hirayama, 1964	193 Japanese children Ambient temperature No dietary information
Meyer et al., 1992	18 prepubescent (PP) and 17 pubescent (P) boys and girls 42°C (107.6°F) and 40 min cycling No dietary information, 1 d

Sodium Concentration in Sweat, mmol/L (g/L)	Sweat Sodium Loss, mmol/d (g/d)
49–180 (1.13–4.20)	122–265 (2.8–6.1)
21–53 (0.48–1.21)	Not determined
10–58 (0.23–1.33)	Not determined
Day 1: 75–100 (1.7–2.3) Day 10: 40–45 (0.92–1.0)	Not determined
Water: 33 (0.76) Saline: 36 (0.83)	Water: 156 (3.6) Saline: 176 (4.0)
35–55 (0.81–1.3)	Not determined
	50 (1.2) 78 (1.8) 105 (2.4)
45–60 (1.0–1.4)	Not determined
5–55 (0.12–1.2)	Not determined
25–35 (0.58–0.80) (PP) 35–40 (0.80–0.92) (P)	Not determined

continued

TABLE 6-3 Continued

Reference	Study Design
Mao et al., 2001	Chinese soccer players, 16–18 yr 32–37°C (89.6–98.6°F) No dietary information, 8 d
Elderly	
Inoue et al., 1999	9 men, 63–67 yr 90 min/d exercise, 43°C (109.4°F) No dietary information, 8 d

Chloride Balance

Chloride losses usually accompany sodium losses. Hence conditions and diseases in which sodium is lost are likewise associated with chloride loss. Excess chloride depletion, marked by hypochloremia, results in hypochloremic metabolic alkalosis (a syndrome seen in individuals with significant vomiting), in which loss of hydrochloric acid is the primary form of chloride loss.

Much of the evidence of the effects of chloride deficiency comes from studies in the 1980s of infants who inadvertently consumed formulas that were manufactured incorrectly with low chloride content (CDC, 1979, 1980; Roy and Arant, 1979). Clinical symptoms and signs noted with the ensuing hypochloremia included growth failure, lethargy, irritability, anorexia, gastrointestinal symptoms, and weakness (Grossman et al., 1980). Some infants presented with hypokalemia, metabolic alkalosis, hematuria, hyperaldosteronism, and increased plasma renin levels (Roy, 1984). Long-term consequences to the infants of consuming the infant formulas that were inadequate in chloride have been evaluated as well (Malloy et al., 1991; Roy and Arant, 1981; Willoughby et al., 1990). Developmental screens were used to evaluate the infants (Willoughby et al., 1990), which indicated some delay in speech development. Follow-up after 9 to 10 years in the children indicated that the effects of early growth retardation had vanished and cognitive skills appeared normal, but some deficits in language skills were present in some children (Malloy et al., 1991).

Chloride deficiency is thus rarely seen given that most foods containing sodium also provide chloride, unless special medical products low in chloride are consumed.

Sodium Concentration in Sweat, mmol/L (g/L)	Sweat Sodium Loss, mmol/d (g/d)
55 ± 27 (1.26 ± 0.62)	Not determined
50–90 (1.2–1.9)	Not determined

Serum or Plasma Sodium Concentration

A number of studies have reported the concentrations of serum or plasma sodium by level of dietary sodium intake. Changes in sodium intake can influence serum or plasma levels of sodium, but the changes are relatively small and do not lead to pathological conditions, such as hyponatremia. Studies have shown that low intakes of sodium (0.15 to 0.23 g [6 to 10 mmol]/day) do not result in hyponatremia (defined as plasma sodium levels < 135 mmol/L) in healthy nonhypertensive (Kirkendall et al., 1976; Luft et al., 1979b; Overlack et al., 1995; Roos et al., 1985) or hypertensive individuals (Kempner, 1948; Mark et al., 1975). When observed, hyponatremia is often caused by excessive sodium loss from the body, which occurs with impaired renal function, increased vasopressin release, or excessive consumption of water. Diuretic use is an infrequent cause of hyponatremia. Overall, there is little evidence of any adverse effect of low dietary sodium on serum or plasma sodium concentrations in healthy individuals.

Plasma Renin Activity

Renin is released from the juxtaglomerular cells of the kidney in response to a perceived reduction in blood volume, blood pressure, or tubular sodium concentration. As a result, renin induces the production of angiotensin II, which stimulates renal sodium reabsorption via a direct tubular effect, as well as by increasing the production of aldosterone. In cross-sectional studies, plasma renin activity is inversely associated with sodium intake; the relationship appears to be curvilinear with the greatest rise in plasma renin activ-

ity occurring below a sodium intake of 2.3 g (100 mmol)/day as estimated by urinary sodium excretion (see Figure 6-1). Furthermore, in clinical trials, most of which were brief (2 weeks or less) and had small sample sizes (< 50 participants), reduced sodium intake commonly led to a rise in plasma renin activity (Table 6-4).

Meta-analyses of trials have likewise documented this relationship (Graudal et al., 1998; He and MacGregor, 2002). In a meta-analysis that only included trials lasting for 4 or more weeks and excluding those trials with extremely low sodium intakes, sodium reduction led to an average increase in plasma renin activity of 0.36 ng/mL/hour from a median value of 1.55 ng/mL/hour (He and MacGregor, 2002). In general, groups with the greatest reduction in blood pressure from a reduced sodium intake are those who concomitantly experience less of a rise in plasma renin; these groups include hypertensive individuals (He et al., 2001; Weinberger et al.,

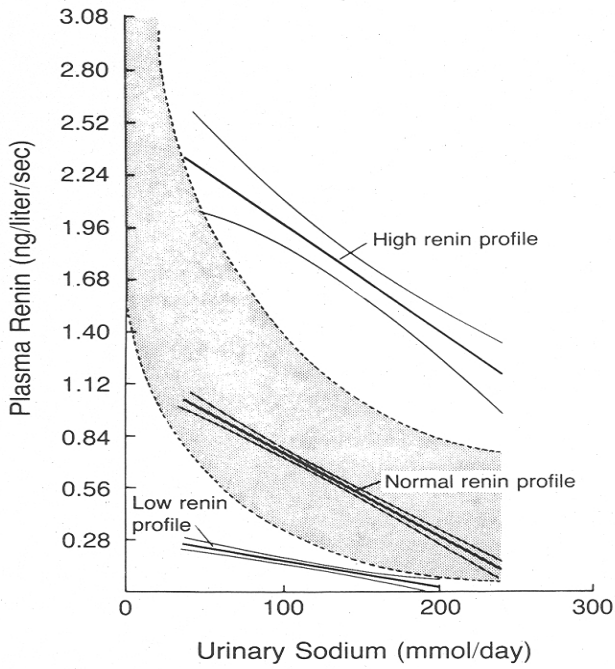

FIGURE 6-1 Association between plasma renin activity and urinary excretion of sodium in patients with hypertension. The normal range of the relation of plasma renin activity to daily urinary sodium is indicated by the shaded band. Reprinted with permission, from Alderman et al. (1991). Copyright 1991 by the Massachusetts Medical Society.

1986), African Americans (He et al., 1998; Weinberger, 1993; Weinberger et al., 1986), and older individuals, both nonhypertensive and hypertensive (Weinberger and Fineberg, 1991). In one prospective observational study, an elevated renin/sodium profile (plasma renin activity of 7.1 ng/mL/hour and urinary sodium excretion of 100 mmol/day or plasma renin activity of 5 ng/mL/hour and 200 mmol/day) was associated with a significantly higher risk for myocardial infarction in hypertensive men (Alderman et al., 1991). However, the number of events was small, just 27, and no other study has replicated these findings. In contrast, in another study of primarily nonhypertensive individuals (Meade et al., 1993), no relationship was found between plasma renin activity and the incidence of myocardial infarction or sudden death from coronary causes. In this study, there were 86 ischemic heart disease events.

Plasma renin activity has also been reported to be associated with left ventricular hypertrophy and insulin resistance (Aronow et al., 1997; Koga et al., 1998, Townsend and Zhao, 1994). A high renin profile has been associated with other cardiovascular risk factors, including elevated plasma cholesterol and triglyceride concentrations and lower high-density lipoprotein concentrations (Allikmets et al., 1996).

The clinical relevance of a rise in plasma renin activity in response to blood pressure reduction is uncertain. Plasma renin activity commonly rises in response to therapies that lower blood pressure and cardiovascular disease risk. For example, thiazide diuretic therapy commonly leads to a rise in plasma renin activity (Niarchos et al., 1984). Yet despite this rise, diuretic therapy has been repeatedly shown to prevent stroke and coronary heart disease (Psaty et al., 2003). In a meta-analysis of 42 trials that compared the effects of seven different classes of antihypertensive medications, the net effects on coronary heart disease of low-dose thiazide diuretics (which raise plasma renin activity) and angiotensin converting enzyme inhibitors (which lower plasma renin activity) were identical (relative risk of 1.0).

Some investigators have interpreted the rise in plasma renin activity from a reduced sodium intake as a deleterious response that mitigates the potential benefits of sodium reduction on blood pressure (Alderman et al., 1991). While this concern is theoretically plausible, there is insufficient evidence in support of this claim. Furthermore, in contrast to blood pressure, which is a well-accepted cardiovascular risk factor, there is no such consensus on the interpretation of plasma renin activity and its role in guiding nonpharmacological or pharmacological therapy for high blood pressure.

TABLE 6-4 Intervention Studies of the Effect of Sodium Intake on Plasma Renin Activity

Reference	Study Design[a]
Nonhypertensive individuals	
Grim et al., 1977	114 men and women Before and after 2 L intravenous saline infusion
Luft et al., 1979b	14 men 3-d crossover
Sullivan et al., 1980	27 men and women 4-d crossover
Zemel et al., 1986	16 African-American men and women 2-wk crossover
Lijnen et al., 1987	10 men 16-wk crossover
Lawton et al., 1988	13 men and women 6-d crossover
Hargreaves et al., 1989	8 men 2-wk parallel
Sagnella et al., 1990	6 men and women, low sodium intake for 4 d; sodium increased by 1.2 g/d (50 mmol/d) over a 7-d period to 8.0 g/d (350 mmol/d) 1–2 d
Ruppert et al., 1991	98 salt-resistant men and women 7-d crossover
Cappuccio et al., 1997	18 men and women 4-wk crossover
Hypertensive individuals	
Mark et al., 1975	6 men with borderline HT 10-d crossover

Dietary Sodium, g/d (mmol/d)	Urinary Sodium,[b] g/d (mmol/d)	Plasma Renin Activity, (ng/mL/h)
3.5 (150)	3.5 (150)	1.7
10.5 (458)	7.7 (335)	0.3
0.23 (10)	0.34 (15)	3.9
6.9 (300)	6.4 (278)	0.9
13.8 (600)	12.5 (543)	0.6
18.4 (800)	16.2 (706)	0.4
27.6 (1,200)	25.9 (1,122)	0.2
34.5 (1,500)	33.2 (1,443)	0.2
0.23 (10)	0.55 (24)	3.3[c]
4.6 (200)	3.9 (170)	0.7[d]
1 (43)	0.9 (42)	1.4[c]
4 (174)	3.9 (170)	0.6[d]
Low (2 weeks)	0.87(38)	1.6[c]
Low (8 weeks)	5.8 (25)	1.9[c]
Regular	3.4 (147)	0.7[d]
0.23 (10)	0.29 (13)	3.2
9.2 (400)	7.5 (326)	0.3
1.2 (50)	1.1 (49)	2.6[c]
3.4 (150)	3.6 (155)	1.5[d]
0.23 (10)	0.28 (12)	7.1[c]
1.2 (50)	0.29 (13)	7.5[c]
2.3 (100)	0.62 (27)	3.6[d]
3.4 (150)	2.0 (89)	2.0[d]
4.6 (200)	3.9 (169)	1.8[d]
5.8 (250)	6.2 (268)	1.9[d]
8.0 (350)	6.8 (296)	1.1[d]
0.46 (20)	0.39 (17)	2.5 (estimated from figure)
6.9 (300)	6.7 (292)	0.3
	2.0 (91)	1.5[c]
	3.8 (167)	1.2[d]
0.23 (10)		7.3
9.4 (410)		1.7

continued

TABLE 6-4 Continued

Reference	Study Design[a]
MacGregor et al., 1982a	19 men and women with essential HT 4-wk crossover
Watt et al., 1983	13 men and women with mild HT 4-wk crossover
Resnick et al., 1985	12 men and women with essential HT 5-d crossover
Zemel et al., 1986	6 African-American men and women 2-wk crossover
MacGregor et al., 1989	20 men and women with mild HT 4-wk crossover
Del Rio and Rodriguez-Villamil, 1993	30 men and women with essential HT 2-wk crossover
Fotherby and Potter, 1993	17 elderly men and women with essential HT 5-wk crossover
Overlack et al., 1995	46 men and women with essential HT 1-wk crossover
Cappuccio et al., 1997	29 men and women 4-wk crossover

[a] HT = hypertensive.
[b] SS = salt sensitive, SR = salt resistant.
[c,d] Values with different superscripts differed significantly from lowest intake levels at $p < 0.05$.

Accordingly, contemporary guidelines have not recommended routine measurement of plasma renin activity as a means to guide selection of antihypertensive therapy (Chobanian et al., 2003). Further research is needed before plasma renin activity can be used as a marker of adequacy for sodium intake.

Elevation in Blood Pressure

While a reduced sodium intake, on average, lowers blood pressure (see later section, "Adverse Effects of Overconsumption"), the

Dietary Sodium, g/d (mmol/d)	Urinary Sodium,[b] g/d (mmol/d)		Plasma Renin Activity, (ng/mL/h)	
	1.9 (86)		1.7	
	3.7 (162)		0.97	
	1.4 (59)		2.2	
	3.2 (139)		1.2	
0.23 (10)			6.0[c]	
4.6 (200)			1.8[d]	
1 (43)	0.99 (43)		3.2	
4 (174)	4.9 (215)		1.9	
1.2 (50)	1.1 (49)		2.3	
2.3 (100)	2.4 (108)		1.6	
4.6 (200)	4.4 (190)		1.4	
≈ 0.8 (35)	1.1 (48)		3.1[c]	
≈ 4.7 (204)	4.6 (199)		1.3[d]	
	2.2 (95)		1.2[c]	
	4.0 (174)		0.9[d]	
	2.2 (95)		1.2[c]	
	4.0 (174)		0.9[d]	
0.46 (20)	*SS*	*SR*	*SS*	*SR*
6.9 (300)	0.55 (24)	0.44 (19)	1.1[c]	2.8[c]
	6.1 (264)	6.2 (269)	0.1[d]	0.4[d]
	2.2 (95)		1.6[c]	
	4.2 (182)		1.3[d]	

individual blood pressure response is heterogeneous (see Figures 6-2 and 6-3). Certain groups have greater (or lesser) reductions in blood pressure in response to reduced sodium intake. Those with the greatest reductions in blood pressure have been termed "salt sensitive," while those with little or no reduction in blood pressure have been termed "salt resistant." Some investigators have reported that blood pressure might rise in response to sodium reduction, potentially because of activation of the renin-angiotensin-aldosterone system. However, as discussed below, it is difficult to separate a true rise in blood pressure from a rise in blood pressure that occurs because of intrinsic variability in blood pressure. For

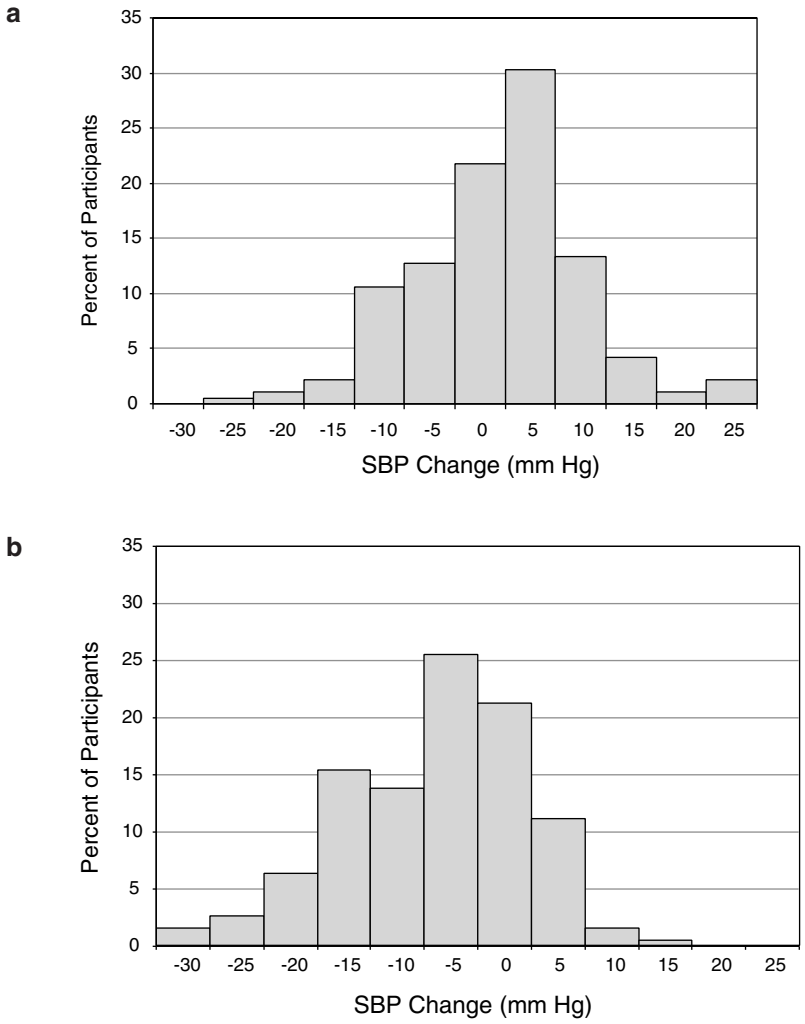

FIGURE 6-2a Distribution of blood pressure differences between two points in time when sodium intake was similar. Each 5 mm Hg bar is centered. SBP = systolic blood pressure. Reprinted with permission, from Obarzanek et al. (2003). Copyright 2003 by the American Heart Association.

FIGURE 6-2b Distribution of blood pressure differences between two points in time when sodium intake decreased by 1.8 g/d (77 mmol/d). Each 5 mm Hg bar is centered. SBP = systolic blood pressure. Reprinted with permission, from Obarzanek et al. (2003). Copyright 2003 by the American Heart Association.

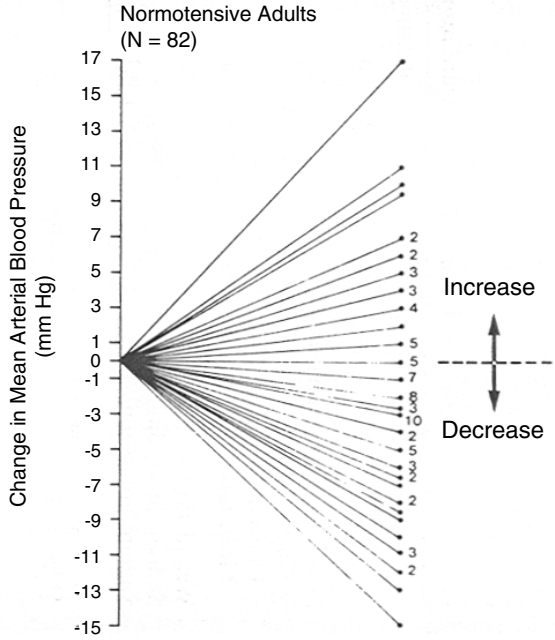

FIGURE 6-3 Mean arterial blood pressure response to dietary sodium reduction. Baseline data is average of five sitting measurements over 12 wk. Change was determined by subtracting baseline from average of six measurements obtained during diet. Reprinted with permission, from Miller et al. (1987). Copyright 1987 by Elsevier Ltd.

the same reason, it is difficult to interpret reductions in blood pressure in a given individual.

In addition to reporting average responses in groups of individuals, some trials have also reported the blood pressure responses of individual participants (Table 6-5). An apparent rise in blood pressure in some individuals when sodium intake is reduced has been interpreted as a pressor response, potentially as a result of an overactive renin-angiotensin-aldosterone system. However, an alternative explanation is that an apparent rise in blood pressure reflects intrinsic blood pressure variability or imprecision in blood pressure measurement. This phenomenon is illustrated by analyses of the Dietary Approaches to Stop Hypertension (DASH)-Sodium trial, which assessed blood pressure change across two points in

TABLE 6-5 Effect of Sodium Reduction on Blood Pressure in Studies Reporting Distribution of Blood Pressure Change in Individuals

Reference	Study Design[a]	Dietary Sodium g/d (mmol/d)
Longworth et al., 1980	82 HT men, 10 d	
Miller et al., 1987	82 NT men and women, 30–58 yr 12 wk	
Ruppert et al., 1991	147 NT men and women, 19–78 yr 7-d crossover	6.9 (300) 0.46 (20)
He et al., 2001	39 NT and 93 HT men and women 5 d	≈ 8.0 (350) 0.23–0.46 (10–20)
Obarzanek et al., 2003	188 NT and HT men and women 4-wk crossover	3.2 (141) 2.4 (106) 1.5 (64)

[a] HT = hypertensive, NT = nonhypertensive.
[b] BP = blood pressure, MAP = mean arterial pressure, SBP = systolic blood pressure.

time, separated by at least a month, when there was no change in diet or sodium level (Figure 6-2a), as well as blood pressure change when sodium was markedly reduced (Figure 6-2b) (Obarzanek et al., 2003). In both situations, there was a wide, Gaussian distribution of blood pressure change. Furthermore, the standard deviation of the distribution of change in blood pressure was similar, 8.4 versus 8.6 mm Hg, respectively, suggesting that much of the variability in blood pressure response to a reduced sodium intake (including an apparent increase in blood pressure in some individuals) results from random factors unrelated to sodium intake. A similar distribution of blood pressure changes was likewise evident in an intervention study (Miller et al., 1987) that measured blood pressure carefully and on multiple occasions pre- and postintervention (see Figure 6-3), as well as in other trials (Ruppert et al., 1991). In such studies, reports that certain individuals experienced a rise in blood pressure (Table 6-5) must be interpreted very carefully. Nonetheless, the group of individuals whose blood pressure

Urinary Sodium g/d (mmol/d)	Findings[b]
4.5 (197) → 1.6 (70)	17% of outpatients and 28% of inpatients has a rise in BP of at least 5 mm Hg
3.6 (157) → 1.6 (68)	≈ 24 (29%) subjects had a rise in MAP ≈ 5 (6%) subjects had no change in MAP ≈ 53 (65%) subjects had a reduction in blood pressure
≈ 6.6 (288) → ≈ 0.39 (17)	25 (17%) subjects had a rise in MAP
≈ 6.9 (300) → ≈ 0.48 (21)	≈ 18/39 (46%) NT subjects had a rise in MAP ≈ 9/93 (10%) HT subjects had a rise in MAP
3.2 (140) → 1.4 (62)	55% had SBP decrease ≥ 5 mm Hg 6% had SBP increase ≥ 5 mm Hg

apparently rises likely differs, on average, from the group of individuals whose blood pressure falls. Specifically, those individuals with an apparent rise in blood pressure experience a greater activation of the renin-angiotensin-aldosterone axis than those whose blood pressure falls (Egan et al., 1994; Weinberger et al., 1993a).

Ruppert and colleagues (1991) reported that while a rise in plasma renin activity and aldosterone concentration were observed in all subjects placed on a reduced sodium diet, the largest increases were observed in those whose blood pressure increased. Those who have the greatest reduction in blood pressure as a result of a reduced sodium intake appear to have a less responsive renin-angiotensin-aldosterone system (Cappuccio et al. 1997; He et al., 1998, 2001; Weinberger et al., 1993a).

Given the above considerations, an apparent rise in blood pressure in response to a reduced sodium intake cannot be used as an indicator of adequate sodium intake.

Blood Lipid Concentrations

Several trials have examined the effects of reduced sodium intake on blood lipid concentrations. Most trials tested the effects of an extremely low intake of sodium, typically 0.46 to 0.69 g (20 to 30 mmol)/day (see Table 6-6). For instance, when 15 healthy men were given a low salt diet of 0.46 g (20 mmol)/day of sodium for 3 weeks, total and low density lipoprotein (LDL) cholesterol concentrations increased by approximately 9 and 12 percent, respectively (Sharma et al., 1990).

Some of these effects have been attributed to a reduced plasma volume because rises in hematocrit, total protein, and albumin concentrations have been noted (Weder and Egan, 1991). However, increases in serum total and LDL cholesterol and triglyceride concentrations persist even after adjustment for changes in hematocrit (Ruppert et al., 1994). A meta-analysis documented statistically significant increases in total and LDL cholesterol concentrations in response to the typically extreme reductions in sodium tested in 13 of the 19 trials (Graudal et al., 1998). A subsequent meta-analysis that focused on trials of "modest" sodium reduction (an average of 1.7 g [75 mmol]/day) did not find significant changes in total, LDL, or high density lipoprotein (HDL) cholesterol concentrations (He and MacGregor, 2002). In the only available trial with three levels of sodium intake—1.1 g (50 mmol)/day, 2.3 g (100 mmol)/day, and 3.4 g (150 mmol)/day—there were no significant changes in fasting blood lipid concentrations by sodium level in either a typical American diet (higher in fat) or the DASH diet (lower in fat) (Harsha et al., 2004). This trial was a controlled, isocaloric feeding study.

Insulin Resistance

A possible adverse effect of reduced sodium intake on insulin resistance has been postulated, potentially as a result of increased sympathetic nervous system activity. It has also been hypothesized that this phenomenon might be more prevalent in certain subgroups—those individuals who experience little or no reduction in blood pressure from a reduced sodium intake (salt-resistant individuals) (Egan and Stepniakowski, 1997).

Empirical evidence on this topic is sparse. A few predominantly small trials have evaluated the effects of reduced sodium intake on insulin resistance and glucose intolerance (see Table 6-7). Several of these trials tested the effects of extremely low sodium intakes

(< 0.7 g [30 mmol]/day). None used a glycemic clamp or minimal model technique to assess insulin sensitivity. In a crossover trial with one-week periods, a sodium intake of 0.46 g (20 mmol)/day, when compared with an intake of 4.8 g (208 mmol)/day increased fasting plasma insulin concentrations and thus decreased the glucose: insulin ratio (Weder and Egan, 1991). In another study with 147 nonhypertensive individuals, a sodium intake of 0.46 g (20 mmol)/day increased serum insulin, but had no effect on serum glucose concentrations compared with an intake of 6.9 g (300 mmol)/day (Ruppert et al., 1991). In a crossover trial with 13 participants, a sodium intake of 0.46 g (20 mmol)/day increased vascular insulin resistance compared with an intake close to 5.5 g (240 mmol)/day (Feldman et al., 1996). These limited data suggest that an extremely low intake of sodium may, in the short-term, be associated with insulin resistance.

Likewise, few studies have examined the effects of sodium intakes at or above 1.2 g (50 mmol)/day. In a randomized crossover study with 34 participants (Grey et al., 1996), there were no significant differences in the glucose:insulin ratio or insulin sensitivity at a sodium intake of 1.2 g (52 mmol)/day and 4.2 g (185 mmol)/day. Two other smaller trials (Boero et al., 2000; Schorr et al., 1996) reported no effects of sodium reduction on measures of insulin resistance from sodium reduction. In contrast, in a crossover study of eight individuals, sodium reduction to 1.7 g (75 mmol)/day from 5.4 g (235 mmol)/day resulted in systemic insulin resistance as assessed by fasting glucose:insulin ratio (Feldman and Schmidt, 1999). In another trial, the total glycemic response to an oral glucose tolerance test was 8 percent lower on the higher of the two sodium intakes (6.1 versus 3.1 g [267 vs. 135 mmol]/day) (Ames et al., 2001).

Overall, available evidence on the effects of sodium reduction on insulin resistance is sparse and inconsistent. Longer-term studies at relevant sodium intakes are needed to assess the effects of sodium intake on insulin resistance.

FACTORS AFFECTING SODIUM AND CHLORIDE REQUIREMENTS

Physical Activity and Temperature

Physical activity can potentially affect sodium chloride balance, mostly from increased losses in sweat. Individuals who exercise

TABLE 6-6 Effect of Sodium Reduction on Blood Cholesterol Concentrations in Order of Increasing Duration of Intervention

Reference	Study Design
Nonhypertensive (NT) individuals	
Ruppert et al., 1994	163 men and women, 19–78 yr 1-wk crossover
Grey et al., 1996	34 men 1-wk crossover
Sharma et al., 1990	15 men, 20–31 yr 3-wk crossover
Schorr et al., 1996	21 men and women 4-wk crossover
Hypertensive (HT) individuals	
Masugi et al., 1988	8 patients with essential HT 5-d parallel
Del Rio et al., 1993	30 men 2-wk crossover
Boero et al., 2000	13 men and women, 21–64 yr 2-wk crossover
Grobbee et al., 1987	40 young adult men and women with mildly elevated blood pressure 6 wk
Geleijnse et al., 1995	89 men and women, 55–75 yr 24-wk parallel
Nonhypertensive and hypertensive individuals	
Harsha et al., 2004	390 men and women 4-wk crossover feeding study

[a] LDL = low-density lipoprotein, HDL = high-density lipoprotein, TC = total cholesterol.

[b] Differed significantly at $p < 0.05$.

Sodium Intake or Urinary Sodium g/d (mmol/d)	Cholesterol Concentration (mmol/L)[a]
300 → 20	Total and LDL cholesterol greater in counter-regulators with sodium reduction
185 vs. 52	No difference in total or LDL cholesterol
220 → 20	Total cholesterol 4.26 → 4.52[b] LDL cholesterol 2.86 → 3.13[b] HDL cholesterol 0.89 → 0.85
105 vs. 175	No difference in total, LDL, or HDL cholesterol
171 → 34	Total cholesterol 5.8 → 6.5[b] LDL cholesterol 1.46 → 1.7[b]
199 → 48	Total cholesterol 5.53 → 5.78 HDL cholesterol 1.24 → 1.17[b]
1.2 (50) 5.8 (250)	No significant differences in total and HDL cholesterol
1.3 (57) 2.9 (129)	4.8 4.8
143 → 102	No significant difference in the serum HDL/total cholesterol ratio

DASH Diet			
(n = 197)	*TC*	*LDL*	*HDL*
1.5 (65)	191	124	45
2.4 (106)	189	123	45
3.3 (143)	191	123	45
Control Diet			
(n = 193)	*TC*	*LDL*	*HDL*
1.5 (65)	208	138	48
2.4 (106)	206	135	48
3.3 (143)	207	136	49

TABLE 6-7 Effect of Sodium Reduction on Glucose Intolerance

Reference	Study Design[a]	Sodium Intake g/d (mmol/d)
Ruppert et al., 1991	147 NT men and women, 19–78 yr 7-d crossover	0.46 (20) 6.9 (300)
Weder and Egan, 1991	9 NT and 18 HT men, 23–55 yr 7-d crossover	0.46 (20) 4.8 (208)
Feldman et al., 1996	5 NT and 8 HT men 1-wk crossover	0.46 (20) 5.5 (240)
Grey et al., 1996	34 NT men 1-wk crossover	1.2 (52) 4.2 (185)
Schorr et al., 1996	21 NT men and women 4-wk crossover	2.4 (105) vs. 4.0 (175)
Feldman and Schmidt, 1999	8 NT men, 25–40 yr 1-wk crossover	1.7 (75) 5.4 (235)
Boero et al., 2000	13 HT men and women, 21–64 yr 2-wk crossover	5.8 (250) 1.2 (50)
Ames et al., 2001	21 HT men and women 4-wk crossover	3.1 (135) 6.1 (267)

[a] NT = nonhypertensive, HT = hypertensive.
[b] SS = salt sensitive, Hb = hemoglobin, AUC = area under the curve.
[c] Significantly different.

strenuously in the heat on a daily basis can lose substantial amounts of sodium. The loss of sodium in sweat is dependent on a number of factors, including overall diet, sodium intake, sweating rate, hydration status, and degree of acclimatization to the heat (Allan and Wilson, 1971; Allsopp et al., 1998; Brouns, 1991). The amount of sodium lost in sweat is less in those acclimatized to the heat than in

Findings[b]		
Insulin (μU/mL) (SS) 10.4[c] 7.9[c]		
No difference in glucose concentration		
Insulin (μU/mL) 14.5[c] 11.5	*Glucose (mg/dL)* 95.9 96.6	*Glucose/Insulin Ratio (mIU/mmol)* 7.8[c] 10.9[c]
Plasma glucose (mmol/L) 4.9–5.2 4.6–5.2	*Glycated Hb (%)* 3.9–4.8 4.0–4.9	Vascular sensitivity to insulin reduced when fed low salt diet
Plasma glucose (mmol/L) 4.85 4.85		*Glucose/insulin ratio (mIU/mmol)* 1.5 1.4
No significant difference in the AUC for glucose or insulin		
		Glucose/insulin ratio (mIU/mmol) 0.6[c] 1.2[c]
No significant differences in serum glucose concentration		
Glycemic response on a glucose tolerance test was 8.0% lower during sodium supplementation; $p < 0.001$		

those who are not (Sawka and Montain, 2000). Sodium sweat loss was reported to be significantly greater when subjects performed a running exercise than when the subjects sat in a climatic chamber at 40°C (104°F) (123.1 ± 33.6 mmol [2.8 ± 0.8 g]/L versus 84.3 ± 31.5 mmol [1.9 ± 0.7 g]/L, respectively) (Fukumoto et al., 1988). Exposure to heat without exercise, however, also alters sweat so-

dium concentration. Overall, sweat sodium concentration averages about 35 mmol/L, with a range from 10 to 70 mmol/L (Sawka and Montain, 2000; Verde et al., 1982).

In a classical study, Consolazio and colleagues (1963) assessed the sweat sodium losses of three healthy young men who were exposed to 37.8°C (100°F) heat for 7.5 hours/day for 16 days. Average sweat sodium losses fell from 487 mmol (11.2 g)/day (day 1) to 71 mmol (1.64 g)/day (day 11). Due to the individual variation of sweat sodium losses, there was not a concomitant decrease from day 1 to day 16; however, there was a decline in sweat loss over time, demonstrating that acclimation that occurred over a short period of time.

The joint effects on sodium loss of physical activity (or temperature) with dietary sodium intake has received little attention. Only one experimental study in Table 6-3 (Allsopp et al., 1998) reported sodium sweat loss in men given one of three different sodium intakes, all of whom were exposed to heat. Sodium sweat loss fell in those on the lowest sodium intake level (1.5 g [66 mmol]/day), and sodium balance was achieved.

Despite the dearth of empirical studies, there is little reason to expect that a reduced sodium intake would affect the ability to perform physical activity. Several isolated, physically active populations have extremely low intakes of sodium (Oliver et al., 1975; Rose et al., 1988).

Effects of Nutrients on Urinary Losses of Sodium

Potassium

Administration of potassium salts has been shown to increase urinary sodium excretion (for review, see Liddle and coworkers, 1953). In normal human volunteers studied under controlled metabolic conditions, both potassium bicarbonate and potassium chloride have demonstrated substantial and comparable effects on increasing urinary sodium excretion (van Buren et al., 1992), at least acutely until equilibration is reached. At a new steady state, sodium intake and excretion become equivalent. Animal experiments suggest that potassium may inhibit sodium reabsorption in the distal tubule of the kidney (Brunette et al., 1992; Vander, 1970; Young et al., 1976). By reducing extracellular volume and plasma volume, this effect is generally considered to be an important component of the antihypertensive effect of potassium, particularly in patients with hypertension.

While some studies have shown increased urinary sodium excretion with increased potassium intakes (Barden et al., 1991; Gu et al., 2001; Krishna et al., 1989; MacGregor et al., 1982b; Matlou et al., 1986; Smith et al., 1992), other studies have not shown a significant effect with potassium supplementation of up to 4.7 g (120 mmol)/day on urinary sodium excretion (Barden et al., 1986; Brancati et al., 1996; Fotherby and Potter, 1992; Lawton et al., 1990; Overlack et al., 1991; Sacks et al., 2001; Whelton et al., 1995). These studies that have not documented an effect of high potassium intake on sodium excretion may not have measured urinary loss at the appropriate period. The absence of an effect after a new equilibrium was achieved would not preclude an early effect of increased potassium intake.

Calcium

A substantial body of evidence has documented that higher intakes of sodium result in increased urinary excretion of calcium (Breslau et al., 1982; Castenmiller et al., 1985; McCarron et al., 1981). Data on the effect of calcium intake on sodium excretion, however, are limited. When placed for one week each on a low calcium (200 mg/day) diet or a high calcium (1,800 mg/day) diet, there was no difference in the urinary excretion of sodium (Cappuccio et al., 1986). A similar lack of effect of calcium supplementation on urinary sodium excretion was seen over a longer (8 week) period in a crossover trial in which 1.5 g/day of supplemental calcium was compared with a placebo in 46 nonhypertensive and hypertensive subjects (Weinberger et al., 1993b).

Diuretics

Diuretics increase the urinary excretion of water, sodium, and chloride. As a result, hyponatremia and hypochloremia have been observed with the use of diuretics (Gross et al., 1988; Oles and Denham, 1984; Orinius, 1984). In some individuals, typically older white women, severe hyponatremia has been reported as an idiosyncratic response to thiazide-type diuretics (which act on the proximal tubule). This appears to be a consequence of impaired water excretion rather than excessive sodium loss since it can be corrected by water restriction. The hyponatremic affect of thiazide-type diuretics is often observed with the concomitant use of other medications (e.g., furosemide, chlorpropramide, carbamazepine) (Kalksma and Leemhuis, 2002).

Cystic Fibrosis

Cystic fibrosis (CF) is a relatively common genetic disorder in which the body produces abnormally thick and viscous mucus due to the faulty membrane transport of sodium chloride. Several organs, particularly the lungs and pancreas, are affected. As a result, the sodium and chloride content of sweat is very high. In one study, mean sweat sodium or chloride concentrations of CF patients was 104 ± 26 mmol/L compared with 16 ± 7 mmol/L in healthy persons (Pillion and Meezan, 1985). In another study, concentrations ranged from 60 to 150 mmol/L for CF patients while the range was 9 to 72 mmol/L for healthy individuals (Carter et al., 1984). Although the increased amount of sodium and chloride required is unknown in CF patients, the requirement is higher for those CF patients who exercise and therefore have additional losses via sweat (Kriemler et al., 1999).

Diabetes

Diabetes is associated with hyperglycemia and glycosuria when the renal threshold for glucose reabsorption is exceeded. The osmotic effect of glucose on the renal tubule is associated with a passive increase in the renal excretion of sodium and water. In acute situations, when the hyperglycemia is marked (e.g., diabetic ketoacidosis), volume depletion, hypotension, and hyponatremia may occur. This is generally corrected by the intravenous administration of sodium chloride and water, as well as insulin, to reduce the elevated blood glucose levels. While there is some evidence that an extremely reduced sodium intake to 0.46 g (20 mmol)/day can decrease insulin sensitivity, there is little evidence of the adverse effects of sodium reduction to levels of ≈ 1.2 g (50 mmol)/day in nondiabetic populations (Table 6-7). In trials of sodium reduction in diabetics, there was no evidence of a deterioration in glucose control (Dodson et al., 1989; Mulhauser et al., 1996); however, the number of trials was small, as was their sample size.

High blood pressure and blood pressure-related cardiovascular disease are common in individuals with diabetes. As described subsequently, available evidence indicates that diabetics are a salt-sensitive group of the population. Still, sodium reduction would not be beneficial in some individuals with diabetes. Some oral hypoglycemic medications (e.g., chlorpropramide) used for diabetes have been associated with hyponatremia, presumably related to increased free water reabsorption rather than excessive renal so-

dium loss (Gardenswartz and Berl, 1981). In some elderly individuals with diabetes, hyporeninemic hypoaldosteronism may increase renal sodium loss (Schambelan et al., 1972). These individuals are usually identifiable by elevated serum potassium concentrations.

FINDINGS BY LIFE STAGE AND GENDER GROUP

Infants Ages 0 Through 12 Months

Sodium

There has been limited research on sodium requirements for normal growth and development in humans. Growth failure has been recognized in young children with salt-wasting disorders, such as isolated hypoaldosteronism (Rosler, 1984), thus linking the need for adequate sodium in early life to normal growth. The addition of sodium to infant formula and its presence in commercially processed weaning foods has been the focus of debate since the 1970s. Issues debated have been the extent to which sodium is required in infancy for normal growth and the possibility that adult hypertension results from excess sodium intake during early years (Dahl, 1968; de Wardener and MacGregor, 1980). However, while animal studies indicate that sodium is required in normal growth of neonatal rats (Fine et al., 1987; Orent-Keiles and McCollum, 1940) and pigs (Alcantara et al., 1980), no studies were found that evaluated the effects of varying intakes of sodium on growth or other effects in normal, full-term human infants.

For preterm human infants, the few available studies indicate that sodium is indeed required for normal growth (Al-Dahhan et al., 1984; Bower et al., 1988; Chance et al., 1977). Two of these studies were conducted primarily in preterm infants (Al-Dahhan et al., 1984; Chance et al., 1977), while the other was among early and preterm infants with ileostomies (Bower et al., 1988).

When preterm infants born before 34 weeks gestation were given 92 to 115 mg of sodium per kg/day from 4 to 14 days postpartum, there was improved weight gain compared with infants who received 23 to 34 mg/kg/day of sodium (Al-Dahhan et al., 1984). When very-low-birth-weight premature infants were supplemented with sodium, weight gain was increased in a second study (Chance et al., 1977). Measurement of body water space and dynamic skinfold thickness indicated that the weight gain was partially due to water retention, with the remaining due to increases in lean body mass.

Sodium balance and growth was studied in 11 infants born fol-

lowing 25 to 38 weeks gestation and who subsequently had ileostomies due to necrotizing enterocolitis or meconium ileus (Bower et al., 1988). Ileostomy outputs of the 11 infants ranged from 10 to 58 mL/kg/day. Despite the provision of adequate energy and protein intake, growth failure was seen in 6 of 11 infants whose weights ranged from 1.1 to 3.0 kg; however, growth failure was corrected when the sodium content of the formula (which provided on average 46 mg [2 mmol]/kg/day) was increased to provide approximately 90 to 180 mg (4 to 8 mmol)/kg/day of sodium. Urinary sodium excretion associated with weight gain in those supplemented was episodically 10 mmol (230 mg)/L or more. No infant with a urinary sodium concentration consistently greater than 10 mmol/L had growth impairment in spite of all infants demonstrating metabolic acidosis, thought to be due to the loss of bicarbonate in the ileostomy fluid. Some of the infants also exhibited hyperchloremia, which was corrected with the use of supplemental sodium bicarbonate.

Given that the renal tubules of preterm infants are not mature until near gestational term, causing them to have significant urinary losses of sodium, it is quite possible that the sodium needs of pre-term infants related to growth differ from that of full-term infants. Hence the quantitative impact of sodium intake on growth in healthy, full-term infants cannot be ascertained from the available literature described above.

It has been suggested that changes in extracellular fluid volume in infants in response to sodium intake could be a measure of adequacy of sodium, and possibly excess as well (Bernstein et al., 1990). One study evaluated three groups of full-term infants (> 2.5 kg, born > 37 weeks' gestation) at 6 weeks. One group had been exclusively fed human milk (n = 43 infants), a second group was fed a lower sodium formula (arbitrarily determined to be < 231 mg [10 mmol]/L) (n = 42 infants), and a third group was fed a higher sodium formula (all those above the cutoff of 231 mg [10 mmol]/L) (n = 39 infants). In this study, there were no measurable differences in extracellular fluid as measured by dynamic skinfold thickness or in blood pressure in the three groups.

Animal studies, however, have shown effects of inadequate sodium intake on extracellular fluid expansion and growth. When pair-fed young rats were fed varying levels of sodium postweaning, the estimated requirement was about 6.9 mg (0.3 mmol) of sodium per day, or 0.06 mmol/g of new tissue (Fine et al., 1987). Lower intake levels resulted in a dose-related slowed growth associated with reduced extracellular fluid volume, while plasma concentrations of

sodium, potassium, and chloride remained normal. Decreased body fat, bone, and muscle mass were seen, along with decreased protein deposition in the sodium-deficient animals. The authors concluded that dietary sodium was required in sufficient quantities to permit normal expansion of the extracellular fluid volume that accompanies tissue growth.

Chloride

As stated earlier, chloride requirements are generally met due to the presence of sodium chloride in processed foods and infant formula. However, out of concern for the possible long-term consequences relative to chronic disease, manufacturers no longer add salt to infant formula at levels above that found in human milk, nor is salt added to weaning foods in the United States or Canada beyond that necessary for processing (FDA, 1985; Health Canada, 2003).

Chloride losses can be substantial in infants, and, while rare, usually occur secondary to diarrhea or vomiting as a result of infection or mechanical obstruction, such as pyloric stenosis in infancy (which results in vomiting), or continuous gastric suction with resulting metabolic alkalosis. Bartter's Syndrome, a familial autosomal recessive disease characterized by chronic diarrhea and defective chloride reabsorption, also results in hypochloremia, as can renal tubular disorders and cystic fibrosis in which high rates of sweating and resulting loss of chloride in the perspiration cause inordinate loss of chloride (Bartter et al., 1962). In these cases, the loss of chloride is greater than the loss of cations such as sodium, resulting in a hypochloremia without hyponatremia. In response, the extra-cellular fluid (ECF) is decreased, and the metabolic alkalosis results in increased urinary potassium excretion.

Most of the knowledge of chloride deficiency in normal infants comes from reports of 141 infants less than 12 months old who were inadvertently fed infant formulas that were chloride deficient (< 180 mg [5 mmol]/L of chloride). Their symptoms included failure to thrive, weakness, anorexia, and some possible delayed development (Malloy et al., 1991).

Evidence Considered in Setting the AI

In infants there are no functional criteria in use that reflect a response to varying levels of dietary intake of sodium or chloride; thus it is not possible to derive an estimated average requirement

(EAR) for this age group for either nutrient. Following precedents set for other nutrients (see Chapter 1), recommended intakes of sodium and chloride are thus based on an Adequate Intake (AI) that reflects a calculated mean intake of infants principally fed human milk (0 through 6 months of age), or a combination of human milk and complementary foods (7 through 12 months of age).

Ages 0 Through 6 Months. Using the method described in Chapter 2, the AI for sodium during ages 0 through 6 months is based on the average amount of sodium in human milk that is consumed by this age group. A mean intake 0.12 g (5.2 mmol)/day of sodium is estimated based on the average volume of milk intake of 0.78 L/day (see Chapter 2) and an average concentration of sodium in human milk of 0.16 g/L (7.0 mmol/L) produced during the first 6 months of lactation. This mean concentration of sodium in human milk was calculated using a simple average of the sodium concentration values analyzed in human milk and found in Table 6-8. Chloride is assumed to be adequate in equimolar amounts: 5.2 mmol of chloride is equivalent to 0.18 g of chloride.

Ages 7 Through 12 Months. The AI for sodium for older infants is determined by estimating the sodium intake from human milk (sodium concentration × 0.6 L/day) and from complementary foods (Chapter 2). Sodium intake data (n = 51) from complementary foods are estimated to be 0.29 g (13 mmol)/day based on data from the 1994–1996, 1998 Continuing Survey of Food Intakes of Individuals (CSFII) (see Appendix Table E-5). While data were sparse related to the sodium content of human milk produced by lactating women over 3 months postpartum, in all studies examined there was a decline in the sodium content compared with earlier stages of lactation. Thus the average sodium concentration in human milk was obtained from those values of sodium content available from lactation at 20 weeks or longer, resulting in an average sodium concentration of 0.13 g/L (5.6 mmol/L) for months 7 through 12 (Table 6-8).

Assuming an average volume consumed of 0.6 L/day for this age group (Chapter 2), the sodium intake from human milk during the second 6 months is approximately 0.08 g (3.5 mmol)/day (0.13 g/L × 0.6 L)/day. Thus, the total sodium intake, which includes the amount from complementary foods, is approximately 0.37 g (16 mmol)/day (0.29 g + 0.08 g/day). Chloride is assumed to be adequate in equimolar amounts: 16 mmol of chloride is equivalent to 0.57 g of chloride.

TABLE 6-8 Sodium Content of Human Milk

References	Study	Stage of Lactation[a]	Sodium Concentration (g/L)[b]
Gross et al., 1980	18 women	1 mo pp	0.20
Picciano et al., 1981	26 women	1 mo pp	0.15
		2 mo pp	0.12
		3 mo pp	0.13
Keenan et al., 1982	14 women	3.5–6 wk pp	0.18
	14 women	8.5–18 wk pp	0.11
	12 women	20–32 wk pp	**0.12**
Lemons et al., 1982	7 women	1 mo pp	0.16
	13 women	1.5 mo pp	0.20 (preterm)
	9 women	> 2 mo pp	0.16 (preterm)
Dewey and Lonnerdal, 1983	20 women	1 mo pp	0.23
		2 mo pp	0.26
		3 mo pp	0.18
		4 mo pp	0.18
		5 mo pp	**0.17**
		6 mo pp	**0.13**
Morriss et al., 1986	52 women	3 wk pp	0.17
		5 mo pp	**0.11**

[a] pp = postpartum.
[b] Bold values also used in determining sodium concentration for months 7 through 12.

Sodium and Chloride AI Summary, Ages 0 Through 12 Months

AI for Sodium for Infants
0–6 months **0.12 g (5 mmol)/day of sodium**
7–12 months **0.37 g (16 mmol)/day of sodium**

AI for Chloride for Infants
0–6 months **0.18 g (5 mmol)/day of chloride**
7–12 months **0.57 g (16 mmol)/day of chloride**

Infant Formula

Current regulations for infant formulas are a minimum of 20 mg/100 kcal (≈ 0.14 g [5.9 mmol]/L for sodium content based on 676 kcal/L) to a maximum sodium content of 60 mg/100 kcal (0.40 g

[17.6 mmol]/L based on 676 kcal/L). The current regulation for chloride content for infant formula is a minimum 55 mg/100 kcal (≈ 0.37 g [10.4 mmol]/L based on 676 kcal/L) to a maximum 150 mg/100 kcal (≈ 1.0 g [28.6 mmol]/L based on 676 kcal/L) (FDA, 1985).

Children and Adolescents Ages 1 Through 18 Years

There is no reason to expect that the sodium requirements of children ages 1 through 18 years would be fundamentally different than that of adults given that maturation of kidneys is similar in normal children by age 12 months of age (Seikaly and Arant, 1992). Thus even young children have the ability to conserve sodium in the face of low levels of dietary sodium.

Evidence Considered in Setting the AI

As for adults, an EAR could not be established because of inadequate data from dose-response studies. Hence an AI was set. Given that little data are available indicating that in normal children, inadequate sodium intakes result in specific identifiable markers, and that, as with adults, normal kidney function can maintain sodium balance at extremes of sodium intake, the AI is set based on meeting nutrient needs for other essential nutrients. The AI is thus extrapolated down from the adult AI of 1.5 g/day (65 mmol/day) using relative energy intake, that is, the average of median energy intake levels of the age groups for adults and for children as the basis for extrapolation (see Chapter 2). Relative energy levels are chosen as the method of extrapolation because the AI for adults is based on an intake of sodium from foods found in the Western diet, which allows for consumption of an adequate diet for other required nutrients.

Based on data from the CFSII, the median energy intake for 1- to 3- and 4- to 8-year-old children in the United States was estimated to be 1,372 and 1,757 kcal/day, respectively (IOM, 2002). Median energy intakes for preadolescent (9 to 13 years) and adolescent (14 to 18 years) boys and girls ranged from 1,877 to 2,226 and 1,872 to 2,758 kcal/day, respectively, and thus were near or within the adult range (1,727 to 2,718 kcal/day). Therefore, their AI is the same as that for adults.

Given the estimated adult median intake value of approximately 2,150 kcal, the value for children 1 to 3 years of age is 1.0 g (42 mmol)/day (1,372 kcal ÷ 2,150 kcal × 1.5 g/day) after rounding.

For children 4 to 8 years of age it is 1.2 g (53 mmol)/day (1,757 kcal ÷ 2,150 kcal × 1.5 g/day) after rounding. Chloride is assumed to be adequate in equimolar amounts to sodium; thus the AI for chloride for children 1 to 3 years of age is 1.5 g (42 mmol)/day and for 4 to 8 years of age is 1.9 g (53 mmol)/day.

Sodium and Chloride AI Summary, Ages 1 Through 18 Years

AI for Sodium for Children	
1–3 years	**1.0 g (42 mmol)/day of sodium**
4–8 years	**1.2 g (53 mmol)/day of sodium**
AI for Sodium for Boys	
9–13 years	**1.5 g (65 mmol)/day of sodium**
14–18 years	**1.5 g (65 mmol)/day of sodium**
AI for Sodium for Girls	
9–13 years	**1.5 g (65 mmol)/day of sodium**
14–18 years	**1.5 g (65 mmol)/day of sodium**
AI for Chloride for Children	
1–3 years	**1.5 g (42 mmol)/day of chloride**
4–8 years	**1.9 g (53 mmol)/day of chloride**
AI for Chloride for Boys	
9–13 years	**2.3 g (65 mmol)/day of chloride**
14–18 years	**2.3 g (65 mmol)/day of chloride**
AI for Chloride for Girls	
9–13 years	**2.3 g (65 mmol)/day of chloride**
14–18 years	**2.3 g (65 mmol)/day of chloride**

Adults Ages 19 Through 50 Years

Evidence Considered in Setting the AI

Data are inadequate to set an estimated average requirement (EAR), which requires an indicator of adequacy evaluated at multiple levels of intake, and an assessment of the level at which approximately half of the individuals in the life stage group would demonstrate inadequacy for that indicator. However, available evidence supports an AI of 1.5 g (65 mmol)/day for apparently healthy adults.

First, a diet that provided an average of approximately 1.5 g

(65 mmol)/day of sodium can meet recommended intakes for other nutrients (see Table 6-9) (Craddick et al., 2003; Karanja et al., 1999). The second and third columns of Table 6-9 display the nutrient profiles of two Western-type diets tested in the Dietary Approaches to Stop Hypertension (DASH)-Sodium trial (Sacks et al., 2001): a typical American (control) diet and the DASH diet. Both provided an average sodium intake of approximately 1.5 g (65 mmol)/day (as estimated by mean urinary sodium excretion), while the fourth column provides the current recommended intake for the nutrients listed.

Second, the AI of 1.5 g (65 mmol)/day exceeds the levels of sodium intake (typically < 0.7 g [30 mmol]) that have been associated in some studies with adverse effects on blood lipid concentrations and insulin resistance (Tables 6-6 and 6-7).

Third, this level allows for excess sodium loss in sweat by unacclimatized persons who are exposed to high temperatures or who are moderately physically active. As noted previously, Allsopp and coworkers (1998) documented that heat acclimated persons consuming 1.5 g (66 mmol)/day of sodium achieved sodium balance after 5 days while being exposed to 40°C (104°F) for 10 hours/day (Table 6-2). Extrapolations from this data suggest that on the first day of heat exposure, prior to acclimation, these individuals would have achieved sodium balance if their exposure to 40°C (104°F) heat lasted no more than 6 hours. Specifically, on average, 4.5 mmol (0.1 g) of sodium per hour was lost in sweat during heat exposure prior to acclimation. After 5 days of acclimation, average sodium sweat losses dropped to 2.1 mmol (0.05 g)/hour.

In summary, the AI is set at 1.5 g (65 mmol)/day of sodium for both young men and women based on meeting sodium needs of apparently healthy individuals, as well as that of other important nutrients using foods found in a Western-type diet. It is assumed these individuals are moderately active in temperate climates. This level of sodium is equivalent to 3.8 g/day of sodium chloride, which would also provide 2.3 g (65 mmol) of chloride. This AI does not apply to highly active individuals such as competitive athletes and workers exposed to extreme heat stress because of increased loss of sodium via sweat (see later section, "Special Considerations").

Sodium and Chloride AI Summary, Ages 19 Through 50 Years

AI for Sodium for Men	
19–30 years	**1.5 g (65 mmol)/day of sodium**
31–50 years	**1.5 g (65 mmol)/day of sodium**

TABLE 6-9 Calculated Nutrient Profiles of the Dietary Approaches to Stop Hypertension (DASH) and Typical American (Control) Diets at the Lower Sodium Intake in the DASH-Sodium Trial[a]

Nutrient[b]	DASH Diet	Typical American Diet	RDA or AI*[c]
Protein, g	94.3	74.5	56
Protein, % kcal	18.0	14.3	10–35
Carbohydrate, g	306	256	130
Carbohydrate, % kcal	58.5	49.0	45–65
Total fat, g	63.1	87.1	—
Total fat, % kcal	27.2	37.6	20–35
Saturated fat, g	14.4	35.7	—
Saturated fat, % kcal	6.2	15.4	ALAP[d]
Monounsaturated fat, g	25.9	28.5	—
Monounsaturated fat, % kcal	11.2	12.3	—
Polyunsaturated fat, g	18.1	16.4	18.6*[e]
Polyunsaturated fat, % kcal	7.8	7.1	5.5–11[f]
Cholesterol, mg	128	272	ALAP
Total dietary fiber, g	29.9	10.8	29.4*[g]
Potassium, g	4.5	1.7	4.7*
Magnesium, g	0.50	0.17	0.32
Calcium, g	1,260	453	1,000*
Zinc, mg	12.1	7.7	11
Thiamin, mg	1.7	1.4	1.2
Riboflavin, mg	2.1	1.4	1.3
Niacin, mg	24.1	22.6	16
Vitamin B_6, mg	2.8	1.4	1.3
Vitamin B_{12}, µg	3.8	3.1	2.4
Vitamin C, mg	300	143	90
Vitamin E, mg d-α-tocopherol equivalents	14.0	7.9	15[h]

[a] In the DASH-Sodium trial, the average sodium intake was 1.5 g (65 mmol) as estimated by mean urinary excretion. The sodium intake of each participant was indexed to calorie level (0.9 to 1.8 g/d (39 to 78 mmol, corresponding to 1,600 to 3,600 kcal/d), Svetkey et al. (1999a).

[b] Nutrients not analyzed but for which Recommended Dietary Allowances (RDAs) or Adequate Intakes (AIs) have been established (IOM, 1997, 1998, 2000b, 2001, 2002): chromium, copper, fluoride, iodine, iron, manganese, molybdenum, phosphorus, selenium, vitamin A, vitamin D, vitamin K, folate, pantothenic acid, biotin, and choline.

[c] Average of recommended intake for young adult men and women; AI indicated with *; all others are RDAs.

[d] As low as possible while consuming a nutritionally adequate diet.

[e] AI for men for *n*-3 fatty acids = 1.6 g; for *n*-6 fatty acids = 17 g; total = 18.6 g.

[f] *n*-3 fatty acids = 0.5–1.0 % of kcal; *n*-6 fatty acids = 5–10% of kcal.

[g] Amount listed is based on 14 g dietary fiber/1,000 kcal.

[h] Vitamin E RDA is 15 mg d-α-tocopherol; 1 mg ≈ 1.2 mg d-α-tocopherol equivalents.

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AI for Sodium for Women	
19–30 years	**1.5 g (65 mmol)/day of sodium**
31–50 years	**1.5 g (65 mmol)/day of sodium**
AI for Chloride for Men	
19–30 years	**2.3 g (65 mmol)/day of chloride**
31–50 years	**2.3 g (65 mmol)/day of chloride**
AI for Chloride for Women	
19–30 years	**2.3 g (65 mmol)/day of chloride**
31–50 years	**2.3 g (65 mmol)/day of chloride**

Older Adults and the Elderly Ages 51+ Years

Methods Used to Set the AI

Renal Function. The ability of the kidney to conserve sodium decreases with age in response to varying and thus lower intake of salt decreases with age. The ability of apparently healthy older individuals to adapt by decreasing urinary sodium when fed very low sodium diets (in the range of 0.23 g [10 mmol]/day) has been shown to be much slower than the adaptation seen in younger individuals; however, with time, older individuals were able to adapt and reduce urinary sodium excretion to levels less than 10 mmol/day (Epstein and Hollenberg, 1976). In a study in which individuals over 40 years of age were compared with race-, sex-, and body weight-matched controls below 40 years of age, short-term loading via intravenous saline administration demonstrated distinct age-related differences in sodium excretion, which included excreting significantly more sodium during the night than the younger control subjects (Luft et al., 1980, 1982, 1987).

The clinical significance of this impaired response may be considerable when older individuals must quickly adapt to the reduced sodium intakes that are often seen during illnesses or following surgery. The result of a rapid decrease in sodium and fluid intake is a reduction in extracellular fluid volume, which is clinically manifested as a decrease in circulating blood volume. In clearance studies of apparently healthy younger and older subjects, older subjects had a reduced ability to reabsorb sodium at the distal tubule compared with their younger counterparts (Macias-Nuñez et al., 1978). Possible mechanisms by which distal tubule function is affected include development of interstitial fibrosis (Macias-Nuñez et al., 1980) or loss of functioning nephrons. In addition, the hormonal

changes that occur with age in the kidney, include increased blood flow to the medulla, depressed activity of the renin-angiotensin-aldosterone system (Weidmann et al., 1977), and diminution in the activity of Na^+/K^+-ATPase (Macia-Nuñez et al., 1980), all of which impair distal tubule function.

Alterations in the renin-angiotensin-aldosterone system have been demonstrated with age. In a study of elderly subjects, basal plasma renin concentration was 30 to 50 percent less in the presence of normal levels of renin substrate (angiotensinogen) (Crane and Harris, 1976). Similarly, a 38 percent decrease in plasma aldosterone concentration was noted in 15 elderly, nonhypertensive volunteers (60 to 74 years in age) when reclining while following a lower sodium diet (urinary sodium excretion averaged 124 mmol [2.8 g]/day) when compared with 28 younger counterparts (19 to 29 years of age; urinary sodium excretion was very similar and averaged 121 mmol [2.8 g]/day) (Weidmann et al., 1977). When young and elderly subjects were put through regimens known to stimulate secretion of renin (e.g., moving from a sitting position to standing upright, a very low sodium diet (0.23 g [10 mmol]/day of sodium intake), or furosemide administration), age differences in plasma renin activity were further magnified (Anderson et al., 1980; Crane and Harris, 1976; Cugini et al., 1987; Hall et al., 1989; Luft et al., 1987; Tsunoda et al., 1986; Weidmann et al., 1975).

The age-related suppression of aldosterone appears to be due to decreased renin response rather than to intrinsic adrenal gland deficits, since both plasma aldosterone and cortisol responses when upright were similar in the elderly and younger subjects (Weidmann et al., 1977). Thus, during sodium reduction, angiotensin II action on renin to increase renal tubular reabsorption of sodium may be impaired to a greater extent in the elderly.

Increased blood pressure has been directly associated with increased sodium intake. Blood pressure, on average, rises with increased sodium intake (see subsequent discussion) and with reduced potassium intake (see Chapter 5). The relationship of blood pressure to electrolyte intake has been more highly correlated with the sodium:potassium ratio than either electrolyte alone (Khaw and Barrett-Connor, 1988). Further, an age gradient is evident, such that the rise in blood pressure per unit change in the sodium:potassium ratio is steeper with increasing age (Khaw and Barrett-Connor, 1990). These data, in conjunction with evidence from clinical trials (Vollmer et al., 2001) indicate that sensitivity to salt increases progressively with age and is not just a phenomenon observed in the elderly.

Several trials have documented that reduced sodium intake lowers blood pressure in older adults (Alam and Johnson, 1999; Appel et al., 2001; Cappuccio et al., 1997; Cobiac et al., 1992; Johnson et al., 2001; Weinberger and Finberg, 1991; Weinberger et al., 1986). Some trials have directly evaluated the effect of age on blood pressure responses to dietary sodium reduction. Greater reduction in blood pressure in response to reducing dietary sodium levels to less than 1.75 g (75 mmol)/day in adults over 40 years of age (up to age 54) compared with younger adults aged 21 to 39 years has been reported (Miller et al., 1987). Significantly greater systolic blood pressure reduction from a lower (versus higher) sodium intake in persons older than 45 years compared with those 45 years of age or younger has also been noted (Vollmer et al., 2001).

Limited evidence suggests that sodium sweat concentrations in the elderly are not different from those of young adults (Inoue et al., 1999) (see Table 6-3).

Overall, the data cited above provide no firm basis to modify the AI for older persons. Thus the AI for older adults is extrapolated from younger adults based on the combined average for men and women of median energy intakes (which do decrease with age). Median energy intakes for older women based on the CSFII were 1,507 and 1,356 kcal for 51 through 70 years and 71 years and older, respectively; for older men, median energy intakes were 2,109 and 1,773 kcal/day for 51 through 70 years and 71 years of age and older, respectively (IOM, 2002). The median energy intakes for both genders were averaged.

In summary, extrapolating from younger individuals based on energy intake, the AI is 1.3 g (55 mmol)/day for men and women 51 to 70 years and 1.2 g (50 mmol)/day for those 71 years and older. Chloride is calculated on an equimolar basis: the AI for those 51 through 70 is 2.0 g (55 mmol)/day; for those 71 years of age and older, 1.8 g (50 mmol)/day.

Sodium and Chloride AI Summary, Ages 51+ Years

AI for Sodium for Men	
51–70 years	**1.3 g (55 mmol)/day of sodium**
> 70 years	**1.2 g (50 mmol)/day of sodium**
AI for Sodium for Women	
51–70 years	**1.3 g (55 mmol)/day of sodium**
> 70 years	**1.2 g (50 mmol)/day of sodium**

AI for Chloride for Men

51–70 years	**2.0 g (55 mmol)/day of chloride**
> 70 years	**1.8 g (50 mmol)/day of chloride**

AI for Chloride for Women

51–70 years	**2.0 g (55 mmol)/day of chloride**
> 70 years	**1.8 g (50 mmol)/day of chloride**

Pregnancy

Evidence Considered in Setting the AI

Substantial changes in intracellular and extracellular volume occur during pregnancy. Plasma volume increases approximately 1.3 L, while the interstitial space expands approximately 1.7 L by the end of pregnancy. This increase, plus an increase of approximately 2 L in intercellular water, constitute the absolute physiological hypervolemia of gestation (Chesley, 1978; Hytten, 1980; Lindheimer and Katz, 1985, 2000). There are major differences of opinion on the interpretation of these volume changes that occur during normal pregnancy and their relationship to sodium intake and thus requirements.

Consensus with regard to what constitutes normal kidney function and the role of sodium in maintenance of total body water volume during pregnancy is lacking (Brown and Gallery, 1994; Durr and Lindheimer, 1999; Duvekot et al., 1993; Lindheimer and Katz, 2000; Schrier and Briner, 1991; Steegers et al., 1991a). The mechanism by which the kidneys of pregnant women handle filtered sodium and by which they "sense" volume changes remain uncertain.

Sodium Accretion. Healthy pregnant women gain approximately 16 kg during gestation, most of which is gained during the second and third trimester (13.8 kg) (Carmichael et al., 1997). Not all of this added weight can be accounted for by the products of conception, tissues directly concerned with reproduction, or the gain in total body water, as body fat increases as well.

Pregnancy appears to require an accumulation of an extra 2.1 to 2.3 g (900 to 1,000 mmol) of sodium to maintain the increase in plasma volume (≈ 1.3 L) and interstitial space (≈ 1.7 L), and to provide for the products of conception (Brown and Gallery, 1994; Hytten, 1980; Lindheimer and Katz, 2000). Note that this accumulation occurs over a period of 9 months, and even during the pe-

riod of most rapid accumulation, the gain in body weight is barely 69 to 92 g/day. The amount of additional sodium needed (≈ 0.07 g [3 mmol]/day) would be too small to detect in metabolic balance studies.

Sodium Balance. Some studies have detected increases in the appetite for sodium during gestation (Brown and Toma, 1986). In one small study where sodium intake was reduced to approximately 1.2 g (50 mmol)/day, pregnant women gained less weight and manifested smaller increments in cardiac output, but had gestational outcomes similar to women eating unrestricted diets containing approximately threefold more sodium (Steegers et al., 1991b).

Of interest is a study in which pregnant women decreased their sodium intake to approximately 0.23 g (10 mmol)/day (Bay and Ferris, 1979). Under such severe restriction, it is reasonable that in order to meet the additional needs of pregnancy (i.e., retention of ≈ 0.07 g [3 mmol]/day), the urinary sodium excretion level should have resembled that of the urines of individuals who, based on dietary reduction to a similar low level, virtually eliminate sodium from their urines. The pregnant women did not; they actually excreted 23 to 46 mg (1 to 2 mmol)/day more than control nonpregnant women. The pregnant women also failed to gain the anticipated 0.5 kg of weight during the week of the study and actually lost approximately 1 kg. Thus the data of Bay and Ferris (1979) suggest that pregnant women may be prone to subtle salt wasting. Both before and after infusion of isotonic saline during normal pregnancy in the first trimester, plasma renin activity, as well as aldosterone concentration, were increased, and urinary sodium excretion decreased in the pregnant participants compared with the nonpregnant women studied, suggesting increased sodium retention during pregnancy to meet the additional needs (Weinberger et al., 1977).

Renin-Angiotensin-Aldosterone System. Various studies have focused on the roles of volume-influencing hormones and chronic, as well as acute, sodium loading in pregnant women (Brown and Gallery, 1994; Chesley, 1978; Lindheimer and Katz, 1985, 2000; Weinberger et al., 1977). Though circulating concentrations of all elements of the renin system, as well as plasma aldosterone, are increased in pregnant women compared with that observed in nonpregnant patients with primary aldosteronism, the concentrations change appropriately in response to salt reduction, saline loading, or changes in posture—suggesting, rather than being "high," that concentrations of the renin-angiotensin-aldosterone system are appropriate

in pregnancy and are able to respond to homeostatic demands (Weinberger et al., 1977). Though disputed (Weinberger et al., 1977), pregnant women appear to handle acute and large saline loads as high as 9.5 g (410 mmol) (Chesley et al., 1958) as well as that seen in nonpregnant women. At the opposite extreme of sodium intake, it is evident that in cultures with virtually no sodium intake (e.g., the Yanomamo Indians), reproduction occurs with markedly higher levels of plasma renin activity and serum aldosterone compared with that observed in nonpregnant women; no evidence of observable adverse effects of such extreme diets on gestational outcome have been reported (Oliver et al., 1981).

Plasma Sodium Concentration. Plasma sodium concentration decreases 4 to 5 mmol/L during normal pregnancy due to the resetting of the osmotic threshold for arginine vasopressin secretion and thirst to a level ≈ 10 mOsm/kg below nonpregnant values (see Chapter 4). Thus pregnant women should not be considered hyponatremic until concentrations fall to 130 mmol/L or lower. In contrast, values exceeding 140 mmol/L should raise suspicion of hypernatremia. Finally, the propensity of pregnant women to vomit in the first trimester and the possibility that their onset of sweating at a lower temperature may mean they have greater sweat loss and thus greater sodium losses (Clapp, 1991) might also affect plasma sodium concentrations and hence sodium requirements.

Plasma sodium concentration decreases during pregnancy despite the small but positive cumulative sodium balance previously discussed (at its greatest, just a few mg/day). There are also many gestational physiological changes. They include increased glomerular filtration rate and therefore increased filtered sodium; alterations in plasma concentration of hormones that influence sodium excretion, thus labeled as natriuretic (e.g., progesterone, atrial natiuretic peptide) and antinatriuretic (e.g., angiotensin II, aldosterone, desoxycorticosterone); and even physical factors (e.g., oncotic pressure). All of these physiological changes are known to influence kidney function, but how they eventually affect renal sodium handling is still obscure.

Summary. There is a lack of evidence to suggest that sodium requirements of preganat women differ from that of nonpregnant women. The median energy intake of pregnant women (1,978 kcal/day [IOM, 2002]) falls within the range of energy consumed by young men and women (IOM, 2002). Therefore, the AI for sodium for pregnant women is equal to the AI for nonpregnant adolescent

girls and young women. The AI for chloride is set at a level equimolar to sodium.

Sodium and Chloride AI Summary, Pregnancy

AI for Sodium for Pregnancy	
14–18 years	**1.5 g (65 mmol)/day of sodium**
19–30 years	**1.5 g (65 mmol)/day of sodium**
31–50 years	**1.5 g (65 mmol)/day of sodium**
AI for Chloride for Pregnancy	
14–18 years	**2.3 g (65 mmol)/day of chloride**
19–30 years	**2.3 g (65 mmol)/day of chloride**
31–50 years	**2.3 g (65 mmol)/day of chloride**

Lactation

Evidence Considered in Setting the AI

A small amount of sodium is secreted daily in human milk during the first 6 months of lactation (0.12 g [5.2 mmol]/day) (see earlier section, "Infants Ages 0 Through 12 Months"). There is no evidence to suggest that the sodium requirements of lactating women differ from that of nonlactating women. The estimated median energy intake of lactating women (2,066 kcal/day [IOM, 2002]) falls within the range of energy consumed by young men and women (IOM, 2002). Therefore, the AI for sodium for lactating women is set to be equal to that of nonlactating women. The AI for chloride is set at an equimolar amount based on the AI for sodium.

Sodium and Chloride AI Summary, Lactation

AI for Sodium for Lactation	
14–18 years	**1.5 g (65 mmol)/day of sodium**
19–30 years	**1.5 g (65 mmol)/day of sodium**
31–50 years	**1.5 g (65 mmol)/day of sodium**
AI for Chloride for Lactation	
14–18 years	**2.3 g (65 mmol)/day of chloride**
19–30 years	**2.3 g (65 mmol)/day of chloride**
31–50 years	**2.3 g (65 mmol)/day of chloride**

Special Considerations

Influence of Physical Activity or High Temperature on Sodium Requirements

The AIs given above are for individuals who are moderately active in temperate climates. As was discussed in Chapter 4, high levels of activity or exposure to high temperature or humidity results in increased needs for water to replace sweat losses. In these settings, additional sodium above the AI may be required as well, but experimental data are lacking, especially at dietary intakes of 1.5 g (65 mmol)/day.

Still, for most physically active individuals, the AI should be adequate. Of the 1.5 g (65 mmol)/day, only about 0.23 g (10 mmol) is needed to replace insensible losses, exclusive of sweat and urine, in acclimatized individuals. Hence, approximately 1.3 g (55 mmol) is available to replace sodium loss in sweat. This amount should be adequate even in unacclimatized, untrained individuals, depending on the duration of activity and exposure. However, for such individuals who are unacclimatized to a heavy heat load over long periods of time—such as that resulting from infrequent heavy physical activity at high temperature and humidity over several hours—additional sodium may be needed. As stated earlier, the AI does not apply to individuals who lose large volumes of sodium in sweat, such as competitive athletes and workers exposed to extreme heat stress (e.g., foundry workers and fire fighters). Sodium intake invariably rises with increased energy intake in physically active individuals and this increase usually is enough to compensate for sweat sodium losses. However, some individuals in the situations described above can lose excessively large amounts of sodium in sweat and on those occasions they should ingest a diet that contains sodium in excess of the AI.

Impact of the Sodium AI on Iodine Intake

Total iodine intake includes iodine that is naturally present in foods as well as iodine from iodized salt. While iodine from iodized table salt has been available in the United States and Canada since the 1920s, the extent to which iodized salt currently contributes to meeting iodine needs is unknown. Iodide was originally added to table salt in order to address the problem of endemic goiter, a problem found in the Great Lakes region and the Pacific Northwest. Previously, the food supply in these regions was limited to

locally grown foods that were low in iodine due to soil conditions. However, in the United States and Canada, the current food supply is not restricted to locally grown products and now includes foods grown in multiple regions and countries, thus making iodine more available.

A decline in the use of table salt might result in lower levels of iodine intake. However, current national surveys track urinary excretion of iodine, which is considered a good indicator of intake (IOM, 2001). Based on the most recent survey, iodine intake is adequate (CDC, 2002). If iodine intakes appear to decline, food vehicles other than table salt can be considered as a means of providing additional iodine.

INTAKE OF SODIUM

Sources

Sodium chloride (salt) is the primary form of sodium in the diet. Other forms of sodium that contribute to the total sodium content of food include monosodium glutamate (a constituent of soy sauce) and food additives, such as sodium benzoate, sodium nitrite, and sodium acid pyrophosphate. Sodium bicarbonate and sodium citrate (the anion of which is converted in the body to bicarbonate) are ingested as food additives and can be consumed, sometimes in substantial amounts, as antacids and as alkali therapy for correcting or preventing metabolic acidosis, such as that occurring in chronic kidney disease.

Foods that contain higher amounts of naturally occurring sodium are celery (0.10 g [4.3 mmol]/120 g [1 cup diced]), milk (0.12 g [5.2 mmol]/0.24 L [1 cup]), and shellfish, such as scallops (0.072 g [3.1 mmol]/scallop). On average, tap water in the United States contains about 0.05 g (2.2 mmol)/L (0.01 g [0.43 mmol]/8 oz. cup), although the content varies based on geographic location (Hoffman, 1988). Bottled water in the United States generally contains less than 0.01 g (0.5 mmol)/L (0.002 g/8 oz. cup) of sodium (USDA/ARS, 2002). A survey of commercially available North American and European bottled waters found an average sodium content of 0.005 g (0.22 mmol)/L (0.001 g/8 oz. cup) in North American bottled waters, while the average sodium content in European bottled waters was 0.020 g (0.86 mmol)/L (0.004 g/8 oz. cup) (Garzon and Eisenberg, 1998).

Foods that are processed or canned tend to have higher sodium concentrations due to the addition of salt- or sodium-containing

additives during processing. Example of foods that contain high levels of sodium, primarily as sodium chloride added in processing, include luncheon meats and hot dogs (0.55 g/ounce), canned vegetables (0.23 g/one-half cup), processed cheese (0.35 g/slice), and potato chips (0.28 g/oz.). Most breads, baked goods, and breakfast cereals contain about 0.15 to 0.33 g of sodium per serving. For example, a medium (57 g) bagel has 0.30 g of sodium, a serving of cornflakes (21 g) has 0.15 g of sodium, and one slice of bread (28 g) has 0.16 g of sodium.

Sodium chloride and other sodium-containing food additives (such as those mentioned previously) are also present in condiments, such as Worcestershire sauce, soy sauce, ketchup, onion salt, garlic salt, sea salt, and bouillon cubes, usually to enhance the flavor of foods.

While various forms of sodium are often added during food processing to improve flavor, many sodium-containing additives also have functional roles (Marsden, 1980). Sodium chloride added to yeast bread is essential for dough to rise and it helps control the growth of undesirable bacteria and molds. It also functions as a dough conditioner to strengthen the protein in dough (gluten), which allows it to hold air and not collapse. Salt is also added to many frozen foods to preserve texture (Crocco, 1982). Other sodium additives, such as sodium bicarbonate and sodium aluminum phosphate, are used as leavening agents in nonyeast breads.

Sodium chloride decreases the water activity of foods, thus helping to control the growth of pathogenic bacteria (Jay, 1996). Sodium chloride is thus used as a preservative in meats and is necessary to make fermented products (e.g., pickles) (Niven, 1980; Pearson and Wolzak, 1982). A U.S. Food and Drug Administration guidance to the seafood industry for the control of microbiological hazards, *The Seafood HACCP Guide*, recommends the use of a 3.5 percent sodium chloride solution for the control of the pathogen *Clostridium botulinum* in smoked fish (CFSAN, 2001). Many other food additives containing sodium, such as sodium benzoate and sodium bisulfate, function as preservatives in processed foods to extend shelf-life and control microbiological growth (IOM, 2003; Niven, 1980).

Only about 12 percent of the total sodium chloride consumed is naturally occurring (Mattes and Donnelly, 1991). It has been further estimated that the majority (77 percent of total salt) is consumed as a result of processing, while 6 percent is added while eating, 5 percent is added during cooking, and less than 1 percent is consumed from tap water. Because salt is naturally present in only a

few foods, salt reduction does not need to result in inadequate intakes of macronutrients and micronutrients (Korhonen et al., 2000).

Table 6-10 shows a one day menu of 2,200 kcal and its resulting sodium content. This intake level of 2,200 kcal/day is the median intake of adult men and women from the Continuing Survey of Food Intake of Individuals (CSFII), taken in 1994–1996 and 1998 (IOM, 2002). This table illustrates that sodium intake at levels between the AI of 1.5 g (65 mmol)/day and the Tolerable Upper Intake Level (UL) for adults of 2.3 g (100 mmol)/day (see next section, "Adverse Results of Overconsumption") can be achieved by eating a variety of foods and consuming a diet that provides recommended levels of vitamins and mineral elements, as well as recommended amounts of protein, fiber, carbohydrate, and polyunsaturated fatty acids.

Intake

Based on self-reported intake data in the United States from the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) (Appendix Table D-8), the estimated median intake of sodium from foods (not including salt added at the table) varied by age group and ranged from 3.1 to 4.7 g (135 to 204 mmol)/day for men and 2.3 to 3.1 g (100 to 135 mmol)/day for women in the United States. These intake ranges are equivalent to 7.8 to 11.8 g/day of sodium chloride for men and 5.8 to 7.8 g/day of sodium chloride for women. The estimated dietary sodium intakes of both white and African American men and women in the United States were similar (Appendix Tables D-9 and D-10). Median intakes for sodium based on survey data on usual intakes of sodium for ten provinces in Canada in 1990–1999 (Appendix Table F-3) ranged from 2.8 to 3.8 g (122 to 165 mmol)/day for men and 2.0 and 2.5 g (87 to 109 mmol)/day for women. These intake ranges are equivalent to 7.1 to 9.7 g/day of sodium chloride for men and 5.1 to 6.4 g/day for women.

It should be emphasized that these estimates of self-reported sodium intake do not include salt added at the table and thus underestimate sodium intake for many individuals. In contrast to the NHANES and Health Canada data sets, other studies have estimated total sodium intake (including table salt) from urinary sodium excretion. Recent (1997–1999) population-based estimates of sodium intake in the United States derived from 24-hour urine collections documented median urinary sodium excretion for those aged 40 to

TABLE 6-10 Daily Sodium Intake from a Diet Providing 2,200 kcal

Meal	Food/Beverage Consumed	Calories (kcal)	Sodium (mg)
Breakfast	Shredded wheat miniatures (1 cup)	183	8
	Cantaloupe, cubed (½ cup)	27	13
	Milk, 1% (8 oz)	102	122
	Orange juice (6 oz)	82	2
	White toast (1 slice) with unsalted margarine vegetable oil spread (1 tsp)	89	130
	Coffee, black, unsweetened (12 oz)	13	3
	Total for meal	**496**	**278**
Snack	Banana (1 medium)	105	1
	Water (12 oz)	0	7
	Total for meal	**105**	**8**
Lunch	Sandwich with turkey (2 oz), swiss cheese (1 oz), lettuce (2 leaves), tomato (¼″ slice), mayonnaise, (1 tbsp) and whole wheat bread (2 slices)	395	499
	Baby carrots (8)	28	62
	Fig bar cookies (2)	111	112
	Iced tea, brewed, decaffeinated (16 oz)	5	14
	Total for meal	**539**	**687**
Snack	Almonds, dry roasted, unsalted (¼ cup)	206	< 1
	Raisins (¼ cup)	108	4
	Water (12 oz)	0	7
	Milk, 1% (8 oz)	102	122
	Total for meal	**416**	**134**
Dinner	Baked salmon (3 oz)	151	44
	Long-grain brown rice (½ cup cooked)	108	5
	Tossed salad (1½ cups) with safflower oil and vinegar dressing (2 tbsp)	155	54
	Asparagus (6 spears)	20	13
	Dinner roll, whole wheat (1 medium) with unsalted margarine vegetable oil spread (1 tsp)	101	95
	Angel food cake (1 slice) with sliced strawberries (½ cup) and whipped cream topping (2 tbsp)	114	218

continued

TABLE 6-10 Continued

Meal	Food/Beverage Consumed	Calories (kcal)	Sodium (mg)
	Iced tea, brewed, decaffeinated (16 oz)	5	14
	Coffee, decaffeinated (1 cup)	9	2
	Total for meal	**663**	**445**
Daily total		**2,219 kcal**	**1,552 mg** (67.5 mmol)

NOTE: Vegetables and rice were prepared without added sodium. This diet meets the Adequate Intake or Recommended Dietary Allowance for adult men and women for all nutrients for which one has been established (for fiber, it meets the ratio of 14 g /1,000 kcal), and provides energy nutrients within the acceptable macronutrient distribution ranges. To convert mg of sodium to mmol or mEq of sodium, divide the mg by 23 (the molecular weight of sodium). To convert mg of salt to mg of sodium, divide the mg by the percent of salt that is sodium (23/58.5)—39.3%. Nutrient totals may not equal the sum of the parts due to rounding.

FOOD COMPOSITION DATA: USDA Agricultural Research Service, Nutrient Database for Standard Reference, Release 16.

DATA SOURCE: Environ International.

59 years of 183 mmol (4.2 g)/day in men and 142 mmol (3.3 g)/day in women.

Worldwide, there has been even greater variation in sodium intake, ranging from an estimated mean intake of 0.02 g (1.0 mmol)/day in Yanomamo Indians (below the 1st percentile of adults in NHANES III) to over 10.3 g (450 mmol)/day in Northern Japanese (above the 99th percentile of NHANES III) (Oliver et al., 1975; Sasaki, 1964).

There is a lack of data on average sodium intakes during pregnancy and only a few studies have reported sequentially measured urinary sodium excretion. The median sodium intake for pregnant women was 3.48 g (151 mmol)/day in NHANES III (Appendix Table D-8). In the Calcium for Prevention of Preeclampsia study (CPEP), dietary recalls were obtained on the 4,589 participants at recruitment (during weeks 13 to 21 of gestation) (Morris et al., 2001). Daily sodium intake of the 3,125 nonhypertensive pregnant women averaged 4.24 g (184 mmol)/day. Mean sodium excretion in three small serial studies were approximately 2.3 to 3.5 g (100 to 150 mmol)/day (Brown et al., 1988; Steegers et al., 1991b; Wilson et al., 1980). Of note, the populations in the CPEP study

(Morris et al., 2001) and the study conducted by Wilson and colleagues (1980) included a greater proportion of African American and Hispanic women than are in the general population.

In view of the interactive effects of sodium and potassium highlighted in this report, it is useful to examine intakes of sodium and potassium expressed as the ratio of sodium intake (in mmol/day) to potassium intake (mmol/day) for the various lifestage groups. Appendix Table D-11 includes these data from NHANES III. Under 1 year of age, the median sodium:potassium ratio is less than one. The ratio then rises rapidly to just above two for children 4 through 8 years of age, and remains above two into adulthood, but then drops somewhat in middle- and older-aged adults. The progressive rise in this ratio at an early age reflects a greater increase in dietary sodium intake compared with the increase in dietary potassium intake. A similar pattern is present in both men and women.

ADVERSE EFFECTS OF OVERCONSUMPTION

Hazard Identification

Sodium Intake and Blood Pressure

Sodium chloride consumption is one of several dietary factors that contribute to increased blood pressure. Other dietary factors that raise blood pressure are excess weight, inadequate potassium intake, high alcohol consumption, and a suboptimal dietary pattern (see the following sections). Physical inactivity also increases blood pressure. Increased blood pressure is associated with several chronic diseases, including stroke, coronary heart disease, renal disease, and left ventricular hypertrophy.

Cardiovascular Disease and High Blood Pressure. Data from numerous observational studies provide persuasive evidence of the direct relationship between blood pressure and cardiovascular disease. A review of each epidemiologic study is beyond the scope of this report. However, several meta-analyses have aggregated data across these studies (Lewington et al., 2002; MacMahon et al., 1990). The most recent and largest meta-analysis to date pooled data from 61 prospective observational studies that together enrolled almost 1 million adults, including persons with hypertension (Lewington et al., 2002). Individual-level records were available for each participant in each study. Those individuals with pre-existing vascular disease were excluded.

There were 12.7 million person years of follow-up and, of the total number of deaths (122,716), about half occurred as a result of cardiovascular disease (11,960 deaths from stroke, 34,283 from ischemic heart disease, and 10,092 from other vascular causes). As displayed in Figure 6-4, stroke mortality progressively increased with systolic blood pressure (panel A) and diastolic blood pressure (panel B) in each decade of life. Similar patterns were evident for mortality from ischemic heart disease and from other vascular diseases. In analyses that involved time-dependent correction for regression-dilution bias, there were strong, direct relationships between blood pressure and each type of vascular mortality. Importantly, there was no evidence of a blood pressure threshold—that is,

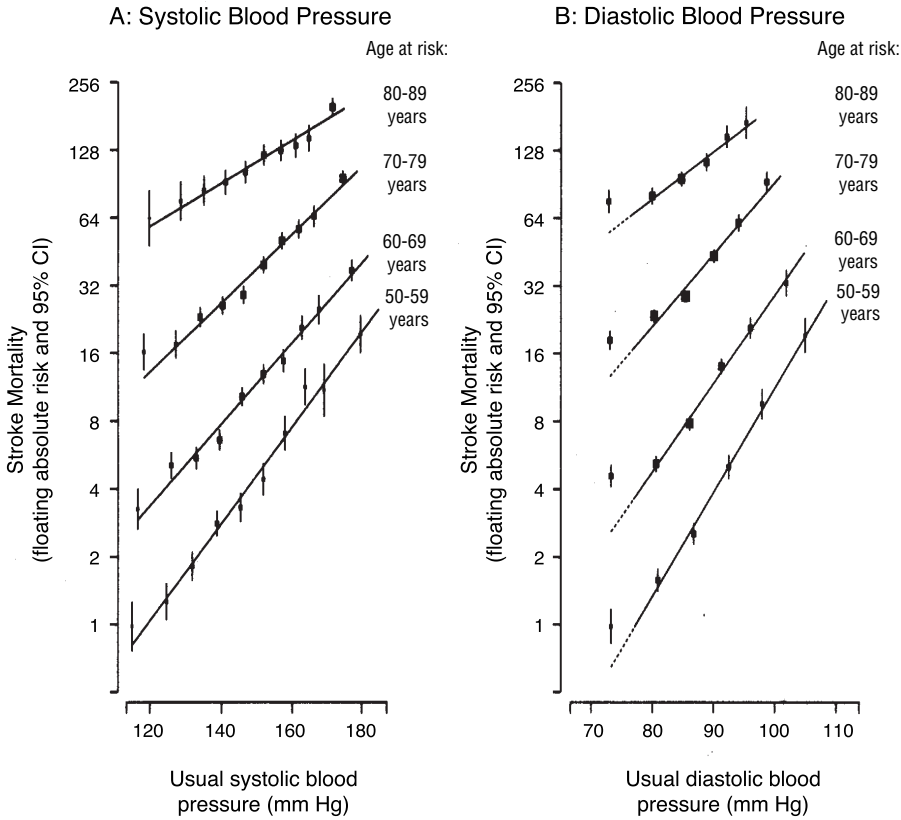

FIGURE 6-4 Stroke mortality rate in each decade of age versus usual blood pressure at the start of that decade. Reprinted with permission, from Lewington et al. (2002). Copyright 2002 by Elsevier Ltd.

vascular mortality increased throughout the range of blood pressures, in both nonhypertensive and hypertensive individuals. Hence, even though currently recommended thresholds for initiation of drug therapy are 140 mm Hg (systolic) and 90 mm Hg (diastolic) for uncomplicated hypertension (Chobanian et al., 2003), these thresholds are operational and do not correspond to a change point in the relationship between blood pressure and cardiovascular disease.

Meta-analyses of clinical trials have conclusively documented that antihypertensive drug therapy reduces the risk of cardiovascular events in hypertensive individuals. For example, reductions in usual diastolic blood pressure of 5, 7.5, and 10 mm Hg were associated with 34, 46, and 56 percent less stroke events, respectively, and 21, 29, and 37 percent less coronary heart disease events, respectively (MacMahon et al., 1990). Overall, the strong direct relationship of blood pressure with cardiovascular disease in nonhypertensive and hypertensive individuals, in conjunction with the well-documented, beneficial effects of antihypertensive therapy, strongly supports efforts to reduce blood pressure in both nonhypertensive and hypertensive individuals and to prevent the age-related rise in blood pressure.

Although only one blood pressure-reduction trial with a clinical endpoint has been conducted in nonhypertensive individuals (PCG, 2001), several analyses have estimated the potential benefits from population-wide application of therapies, such as sodium reduction. For instance, in the United States it has been estimated that a population-wide reduction in systolic blood pressure of 3 mm Hg should reduce mortality from stroke by 8 percent and mortality from coronary heart disease by 5 percent (Stamler, 1991). A 2-mm Hg reduction in diastolic blood pressure would result in a 17 percent decrease in the prevalence of hypertension, as well as a 6 percent reduction in the risk of coronary heart disease and a 15 percent reduction in the risk of stroke and transient ischemic attacks (Cook et al., 1995a). In view of these potential benefits, it is a well-accepted, public health tenet that the optimal strategy to prevent blood pressure-related cardiovascular disease includes population-wide blood pressure reductions through nonpharmacologic therapies in addition to targeted reductions through pharmacologic and nonpharmacologic therapies in hypertensive individuals (Chobanian et al., 2003; Whelton et al., 2002).

Renal Disease and High Blood Pressure. Hypertension is the second leading cause of end-stage renal disease (USRDS, 1999). Observa-

tional studies have shown a direct relationship between blood pressure and renal disease progression (Klag et al., 1996, 1997; Whelton et al., 1996). There is some evidence, albeit inconclusive, that lowering blood pressure may retard the progression of renal disease (Klahr et al., 1994; Peterson et al., 1995). The effect of hypertension on the onset and progression of renal disease has been attributed, in part, to nephrosclerosis (fibrous intimal thickening of the small arteries in the kidney) (Tracy et al., 1988).

Sodium Intake and Blood Pressure: Evidence from Observational Epidemiological Studies. Evidence of a positive association between sodium intake and blood pressure comes from both across-population (ecologic) and within-population observational studies. A strong direct relationship between average salt intake and prevalence of hypertension in a cross-population, ecological study of five geographically diverse communities was reported in 1960 (Dahl, 1960). Subsequently, others have confirmed these findings in larger and more careful studies (Gleibermann, 1973). A strength of these studies is their ability to provide a large contrast in sodium intake, the exposure variable. However, limitations must be acknowledged, including the fact that data were not collected in a standardized fashion. Also, adjustment for potentially confounding variables was either not considered or was inadequate. Despite these constraints, cross-population observational studies tend to indicate that blood pressure and hypertension are lower in societies in which habitual sodium intake is below 1.2 to 2.3 g (50 to 100 mmol)/day, while an increased prevalence of blood pressure and hypertension are observed more frequently in societies with higher habitual levels of sodium intake (Elliott, 1991).

Within-population studies of sodium and blood pressure generally lack statistical power, in large part because of large day-to-day variations in sodium intake and because of imprecise methods (e.g., use of a food-frequency questionnaire rather than a 24-hour urinary sodium excretion to assess sodium intake). Accordingly, results of within-population studies have been inconsistent. Studies with null results include those published by Ascherio and coworkers (1992) and Rastenyte and coworkers (1997) (Table 6-11). Other within-population studies have identified a significant, direct association between urinary sodium excretion (representing dietary intake) and blood pressure (Hajjar et al., 2001; Kesteloot and Joossens, 1988; Khaw and Barrett-Connor, 1988; Liu et al., 2000; Stamler et al., 1997).

As highlighted above, methodological problems hinder an assess-

TABLE 6-11 Epidemiological Studies on Sodium or Salt Intake and Blood Pressure

References	Study Design	Results[a]
Rose et al., 1988; Stamler et al., 1989	Intersalt Study, 10,079 men and women, cross-sectional in 32 countries	Significant positive correlation with urinary Na and slope of blood pressure with age, but not median BP or prevalence of elevated BP In 4 remote locations where sodium intake was very low, BP was low for all ages
Frost et al., 1991	12,773 men and women, cross-sectional data from 14 published studies	Significant association between blood pressure and sodium intake ($p < 0.001$)
Ascherio et al., 1992	Health Professional Follow-up Study, 30,681 US men, prospective cohort, 4-yr follow-up, 1,248 incident cases of hypertension, multivariate analysis	No significant association between hypertension and dietary intake of sodium as assessed by food-frequency questionnaire
Elliott et al., 1996	Intersalt Study, 10,074 men and women, cross-sectional	SBP of individuals was positively associated with sodium excretion
Rastenyte et al., 1997	3,326 Finnish men and women, cross-sectional	No association between urinary sodium and BP in either men or in women
Tunstall-Pedoe, 1999	Scottish Heart Health Study, cross-sectional, $n = 11,629$ men and women	Weak association between urinary sodium and blood pressure
Liu et al., 2000	WHO-CARDIAC Study, 1,151 Chinese and 1,681 Japanese men and women, cross-sectional	SBP was positively associated with sodium excretion in Japanese, while both SBP and DBP was associated with sodium excretion in Chinese

[a] Na = Sodium, BP = blood pressure, DBP = diastolic blood pressure, SBP = systolic blood pressure.

NOTE: Studies include a sample size of at least 1,000 in which urinary sodium was measured.

ment of the true relationship between sodium intake and blood pressure in observational studies. Indeed, with the exception of weight, diet-related risk factors such as sodium are difficult to measure accurately and precisely in individuals. Interview methods have

limitations in reporting, recording, and analysis. Collection of 24-hour urinary excretion for sodium and potassium are objective but are also inconvenient and inevitably incomplete. Importantly, nutrient intakes vary considerably from day to day, so that accurate characterization of an individual's usual intake requires repeated observations over time (IOM, 2000a). Likewise, blood pressure, the outcome variable, should be repeatedly measured because of its intrinsic variability (Obarzanek et al., 2003). There must also be a sufficient range of intakes of the dietary factor under study among members of the population to detect associations of the dietary factor with blood pressure. Finally, relevant confounding variables (i.e., physical activity and other dietary factors) must also be measured precisely. Hence observational studies need repeated, high-quality measurements of relevant variables in large samples of individuals.

One of the largest observational epidemiological studies that followed these guidelines and that explored the relationship between sodium intake and blood pressure was conducted by the Intersalt Cooperative Research Group at 52 centers located in 32 countries (Rose et al., 1988). Urinary sodium, blood pressure, and a number of potentially confounding variables were measured in 10,079 men and women, aged 20 to 59 years, from geographically diverse regions around the world with substantial variation in sodium intake. Repeat measurements of blood pressure and urinary sodium were obtained in a random sample of 807 study participants, allowing for correction of the regression dilution bias associated with variation in day-to-day intake of sodium.

Urinary sodium excretion ranged from 0.0046 g (0.20 mmol)/day (Yanomamo Indians of Brazil) to 5.6 g (242 mmol)/day (Northern China) (Rose et al., 1988). After adjustment for age and gender, sodium excretion and systolic blood pressure were positively associated in 39 of the 52 centers (statistically significant in 15) and negatively associated in 15 centers (statistically significantly in 2). Diastolic blood pressure was positively associated with sodium excretion in 33 centers (statistically significant in 4) and negatively associated in 19 centers (statistically significant in 6). Across the 52 centers, a significant linear relationship was shown between urinary sodium excretion and systolic blood pressure ($p < 0.01$). In cross-population analyses, a highly significant relationship of sodium with the upward slope of blood pressure with age was found across the 52 population samples. The estimated rise in systolic blood pressure with age over a 30-year period (e.g., 25–55 years) was 10 mm Hg less for a 2.3 g (100 mmol)/day lower intake of dietary sodium.

In within-population analyses, after adjustment for age and gender and correction for regression dilution bias, a 2.3-g (100 mmol)/day higher excretion of urinary sodium was associated with a systolic and diastolic blood pressure that was 4.3 and 1.8 mm Hg higher, respectively (Elliott et al., 1996). After additional adjustment for potassium excretion (as an indicator of potassium intake) and alcohol intake, the corresponding values were 6.0 and 2.5 mm Hg. The urinary sodium:potassium ratio was likewise associated with blood pressure and relationships tended to be stronger for this ratio than for sodium alone. Estimates of the association were larger for older compared with younger study participants (Elliott et al., 1996). Cross-population analyses yielded similar results to those noted for the within-person analyses, with a somewhat larger difference in blood pressure for a given difference in urinary sodium excretion.

Effects of Sodium Intake on Blood Pressure: Evidence from Intervention Studies. As previously discussed, a variety of methodological issues complicate the interpretation of observational studies. In this setting, clinical trials are the most appropriate study design to assess the relationship between sodium intake and blood pressure, and numerous trials have evaluated this relationship in nonhypertensive and hypertensive individuals (see Tables 6-12 and 6-13). Trials include controlled feeding studies and behavioral counseling studies. The studies differ in size (< 10 to > 500 persons), duration (range: 3 days to 3 years), extent of sodium reduction, background diet (e.g., intake of potassium), study quality, and documentation. Only 10 trials tested three or more levels of dietary sodium intake (see Appendix I). In the remaining trials, there were just two levels of sodium intake. Study populations also differed in age, race-ethnicity, and other dimensions that might affect the blood pressure response to changes in sodium intake.

Notwithstanding these differences, available trials have provided relatively consistent evidence that a reduced intake of sodium lowers blood pressure in nonhypertensive adults (see Table 6-12). Still, heterogeneity was evident. Some trials did not detect any effect on blood pressure from changes in sodium intake, while other trials recorded substantial reductions in blood pressure. Potential reasons for this heterogeneity include differences in study populations, inadequate statistical power, limited contrast in sodium intake, and other methodological issues. In trials with hypertensive participants (Table 6-13), the extent of blood pressure reduction from a lower intake of sodium was more pronounced than that observed in nonhypertensive participants.

TABLE 6-12 Intervention Studies on Sodium Intake and Blood Pressure in Nonhypertensive Adults in Order of Increasing Duration of Intervention

References	Study Design[a]	Sodium (Na) Intake g/d (mmol)	Na/ Potassium (K) Ratio
Crossover studies			
Luft et al., 1979b	14 men, 3.1 g K (80 mmol) 3–7 d	0.23 (10)	0.13
		6.9 (300)	3.8
		13.8 (600)	7.5
		18.4 (800)	10
		27.6 (1,200)	15
		34.5 (1,500)	19
Sullivan et al., 1980	6 subjects, 2.3 g K (60 mmol) 4 d	0.23 (10)	0.17
		4.6 (200)	3.3
		9.2 (400)	6.6
Bruun et al., 1990	10 men and women, 3.1 g K (80 mmol) 4 d	1.2 (50)	0.62
		4.1 (180)	2.2
		8.7 (380)	4.8
Roos et al., 1985	8 men and women, 3.1 g K (80 mmol) 5 d	0.46 (20)	0.3
		4.6 (200)	2.5
		28.2 (1,228)	15
Lawton et al., 1988	13 men, 3.9 g K (100 mmol) 6 d	0.23 (10)	0.1
		9.2 (400)	4
Sharma et al., 1991	23 men, 2.3 g K (60 mmol) 6 d	0.46 (20)	0.13
		5.5 (240)	1.7
Burnier et al., 1993	23 men, 3.9 g K (100 mmol) 6 d	1.2 (50)	0.5
		4.6 (200)	2.0
Schmid et al., 1990	9 men and women 1 wk	0.46 (20)	
		4.6 (200)	
Egan et al., 1991	9 men 1 wk	0.46 (20)	
		4.6 (200)	
Ruppert et al., 1991	147 men and women, 2.9 g K (75 mmol) 1 wk	0.46 (20)	0.27
		6.9 (300)	4

Urinary Na (mmol/d)	Urinary K (mmol/d)	Blood Pressure SBP/DBP[b] (mm Hg)	
15		113/69	
278		117/70	
543		119/71	
706		121/76	
1,122		125/78	
1,443		131/85	
		p trend < 0.001	
		DBP	*MAP*
20		56[c]	72
143		54[c]	69[c]
412		70[d]	83[d]
45	77	111/68	
181	80	110/65	
386	78	116/69	
220	67	118/76	
202	60	120/74	
1,052	86	121/79	
13	79	110/78	
326	66	112/78	
		SR	*SS*
19–22	61–73	114[c]/73[c]	117[c]/71[c]
265–269	66–84	117[c]/73[c]	123[d]/77[d]
		↓ 1/↓ 4.4	
		↓ 3/↑ 3	
		MAP	
20		93	
210		92	
		MAP	
21		81[a]	
214		80[a]	
		MAP	
		SR	*SS*
17–18		86[a]	86[a]
280–292		86[a]	94[b]

continued

TABLE 6-12 Continued

References	Study Design[a]	Sodium (Na) Intake g/d (mmol)	Na/ Potassium (K) Ratio
Schwartz et al., 1992	11 men, NTN patients; 11 men, HTN patients, 3.9 g K (100 mmol) 1 wk	0.23 (10) 4.6 (200)	0.1 2.0
Fliser et al., 1993	16 men and women 1 wk	0.46 (20) 4.6 (200)	
Overlack et al., 1993	163 white men and women, 2.9 g K (75 mmol) 1 wk	0.46 (20) 6.9 (300)	0.27 4
Sharma et al., 1993	16 men, 2.3 g K (60 mmol) 1 wk	0.46 (20) 5.6 (240)	0.3 4
Feldman et al., 1996	5 subjects, 2.3 g K (60 mmol) 1 wk	0.46 (20) 5.5 (240)	0.33 4
Grey et al., 1996	34 nonobese men 1 wk	< 1.84 (80) + 2.7 (120)	
Fuchs et al., 1987	11 men and women at risk for HT 9 d	0.2–0.4 (9–17) 3.1–4.7 (135–204) 6.2–7.9 (269–343)	
	6 men and women not at risk of HT 9 d	0.2–0.4 (9–17) 3.1–4.7 (135–204) 6.2–7.9 (269–343)	
Skrabal et al., 1981	20 men 2 wk	1.2 (50)/7.8 (200) K 1.2 (50)/3.1 (80) K 4.6 (200)/3.1 (80) K 4.6 (200)/7.8 (200) K	0.25 0.6 2.5 1.0
Skrabal et al., 1984b	52 men, 3.1 g K (80 mmol) 2 wk	1.2 (50) 4.6 (200)	0.6 2.5
Skrabal et al., 1985	62 subjects, 3.1 g K (80 mmol) 2 wk	1.2 (50) 4.6 (200)	0.6 2.5

Urinary Na (mmol/d)	Urinary K (mmol/d)	Blood Pressure SBP/DBP[b] (mm Hg)	
		NTN patients	*HTN patients*
		112[c]/76[c]	118[c]/82[c]
		109[c]/73[c]	114[c]/79[c]
		MAP	
18		80.7[c]	
199		81.3[c]	
		MAP	
		SR	*SS*
≈17	≈74	85.1[c]	83.1[c]
≈289	≈71	84.6[c]	91.2[d]
16		110[c]/55.5[c]	
240		111[c]/56[c]	
		MAP	
6	45	89[c]	
182	40	84[d]	
52		117[c]/71[c]	
185		116[c]/70[c]	
		At risk	
16	49	117/68	
110	28	118/69	
239	36	118/67	
		Not at risk	
8	42	111/70	
103	32	117/68	
245	32	116/67	
28	172	123/69	
40	65	122/70	
210	71	125/73	
155	116	123/69	
		SS	*SR*
≈39	≈88	117[c]/61[c]	118[c]/63[c]
≈191	≈69	125[c]/66[c]	117[c]/62[c]
		At risk	*Not at risk*
36–45	86–87	↓ 5.4/↓ 2.5	↓ 1.0/↓ 0.6
189–199	64–74		

continued

TABLE 6-12 Continued

References	Study Design[a]	Sodium (Na) Intake g/d (mmol)	Na/ Potassium (K) Ratio
Zemel et al., 1986	16 African-American men and women 2 wk	1 (43) 4 (174)	
Sowers et al., 1988	14 African-American men and women 2 wk	0.92 (40) 4.1 (180)	
Johnson et al., 2001	17 elderly subjects, 0.92 g/d (40 mmol/d) Na diet + sodium dose 2 wk	0.92 (40) 2.1 (90) 3.2 (140) 5.5 (240) 7.8 (340)	
Sharma et al., 1990	15 men, 2.3 g K (60 mmol) 3 wk	0.46 (20) 5.1 (220)	0.3 3.7
Kirkendall et al., 1976	8 men, 3.9 g K (100 mmol) 4 wk	0.23 (10) 4.8 (210) 9.4 (410)	0.1 2.1 4.1
Mascioli et al., 1991	48 men and women, provided a placebo or sodium tablets, no diet information 4 wk	+0 +2.2 (96)	
Ruppert et al., 1993	25 men and women, 2.9 g K (75 mmol) 4 wk	1.9 (85) 4.6 (200)	1.1 2.7
Schorr et al., 1996	21 elderly men and women, provided Na-containing beverage or placebo, reduced dietary salt intake < 2.3 g (100 mmol/d) 4 wk	+0 +2.9 g (127)	
Sacks et al., 2001	208 men and women, DASH diet; 204 men and women, control diet 4 wk	*DASH* 2.3 (100) → 1.2 (50) 3.4 (150) → 2.3 (100) *Control* 2.3 (100) →1.2 (50) 3.4 (150) →2.3 (100)	 0.78 → 0.47 1.1 → 0.78 1.5 → 0.9 2.1 → 1.5

Urinary Na (mmol/d)	Urinary K (mmol/d)	Blood Pressure SBP/DBP[b] (mm Hg)
		SBP
42		117[c]
170		122[d]
		MAP
40		81[c]
185		87[d]
75	29	139.4/78.4
136	32	145.5/78.7 ↑ 6.1/↑ 0.3
184	26	153.1/82.4 ↑ 13.7/↑ 4.0
259	35	156.6/82.3 ↑ 17.2/↑ 3.9
359	28	155.9/83.9 ↑ 16.5/↑ 5.5
19	51	106[c]/65[c]
211	55	106[c]/68[c]
		MBP
10	47	90
159	64	88
307	76	90
93		
154		↑ 3.6/↑ 2.3
82		112[c]/73[c]
199		110[c]/73[c]
105		139/84
175		140/84
107 → 67	81 → 81	↓ 1.7/↓ 1.0
144 → 107	75 → 81	↓ 1.3/↓ 0.6
106 → 64	41 → 42	↓ 4.6/↓ 2.4
141 → 106	40 → 41	↓ 2.1/↓ 1.1

continued

TABLE 6-12 Continued

References	Study Design[a]	Sodium (Na) Intake g/d (mmol)	Na/ Potassium (K) Ratio
Cappuccio et al., 1997	18 elderly men 8 wk	≈1.9 (83) ≈3.9 (169)	
Parallel studies			
Hargreaves et al., 1989	8 men 2 wk	1.2 (50) 3.5 (150)	
Cobiac et al., 1992	106 elderly men and women 4 wk	< 1.6 (70 mmol) 3.4 (150)	
Morgan and Anderson, 1987	20 men 6 mo	1.2–1.7 (50–75) Normal diet	
Hypertension Prevention Trial Research Group, 1990	841 men and women, aged 25–49 yr 6–36 mo	Na-kcal n = 126 Control Na reduction alone Na-K n = 196 Control Na reduction alone Na reduction with increased K	 3.3 3.4 3.2 3.3 3.2
Kumanyika et al., 1993	744 men and women, no diet information; behavior change counseling 6–18 mo	Control Na-reduced diet	156 155
He et al., 2000	128 men and women 18–96 mo	Control diet Na-reduced diet	
TOHP Collaborative Research Group, 1997	594 men and women 6–36 mo		3.0

[a] NTN = normotensive, HTN = hypertensive.

[b] SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, SS = salt sensitive, SR= salt resistant.

[c,d] Values with different superscripts differed significantly at $p < 0.05$.

Urinary Na (mmol/d)			Urinary K (mmol/d)			Blood Pressure SBP/DBP[b] (mm Hg)		
91			69			140/81		
167			65			148/85		
49			94			123[c]/63[c]		
155			83			129[c]/66[c]		
						SBP		
≈74						↓ 5.2[a]		
≈150						↓ 2.4[b]		
75[c]						155[c]/90[c]		
155[d]						178[d]/98[d]		
Base	*6 mo*	*36 mo*	*Base*	*6 mo*	*36 mo*	*Base*	*6 mo*	*36 mo*
174	157	183	68	69	68	124.7/83.3	↓ 1.8/↓ 2.5	↓ 2.6/↓ 2.4
171	141	160	65	69	70	124.1/82.9	↓ 3.6/↓ 3.4	↓ 2.3/↓ 2.3
165	150	165	66	66	64	123.9/83	↓ 2.1/↓ 3.0	↓ 2.9/↓ 3.0
163	127	147	64	65	68	124.0/82.6	↓ 3.8/↓ 3.4	↓ 2.8/↓ 2.8
160	117	138	63	69	67	124.1/82.3	↓ 3.4/↓ 3.7	↓ 4.1/↓ 3.7
159	147	63				125.1/83.9	↓ 3.8/↓ 2.9	↓ 3.0/↓ 3.2
103	99	62				124.8/83.7	↓ 5.9/↓ 3.9	↓ 5.1/↓ 4.4
Base	*18 mo*	*6–8 yr*				*Base*	*18 mo*	*6–8 yr*
148	128	148				122.6/84.2	↓ 2.4/↓ 5.6	↑ 2.2/↓ 5.3
148	95	137				122.7/83.8	↓ 5.7/↓ 7.2	↓ 1.6/↓ 7.5
Base	*6 mo*	*36 mo*	*Base*	*6 mo*	*36 mo*	*Base*	*6 mo*	*36 mo*
186	108	135	66.8			127.7/86.1	↓ 5.1/↓ 4.4	↓ 0.7/↓ 3.0

TABLE 6-13 Intervention Studies on Sodium Intake and Blood Pressure in Hypertensive Adults, in Order of Increasing Duration of Intervention

References	Study Design[a]	Sodium (Na) Intake g/d (mmol/d)	Na/ Potassium (K) Ratio
Crossover studies			
Kempner, 1948	Kempner rice diet, 400–500 patients with HT vascular disease 4–898 d	≈0.15 (6)/ 2,000 kcal	
Bruun et al., 1990	12 men with essential HT 3.1g K (80 mmol) 4 d	1.2 (50) 4.1 (180) 8.7 (380)	0.62 2.2 4.7
Resnick et al., 1985	12 adults with essential HT 2.3 g K (60 mmol) 5 d	0.23 (10) 4.6 (200)	0.16 0.3
Shore et al., 1988	6 adults with essential HT 0.23 g Na (10 mmol) diet plus 2.8 g (120 mmol) Na supplements 3.1g (80 mmol) K 5 d	0.23 (10) 2.9 (130)	0.12 1.6
Buckley et al., 1994	12 men and women with essential HT 5 d	0.23 (10) 8.0 (350)	
Lawton et al., 1988	9 men with borderline HT 3.9 g K (100 mmol) 6 d	0.23 (10) 9.2 (400)	0.1 0.25
Kawasaki et al., 1978	19 men and women 2.7 g K (70 mmol) 1 wk	0.21 (9) 5.7 (249)	0.13 3.6
Egan et al., 1991	18 men 1 wk	0.46 (20) 4.6 (200)	
Zoccali et al., 1994	15 men and women with mild HT 2.5 g K (65 mmol) 1 wk	1.2 (50) 4.6 (200)	0.77 3.1

Urinary Na[b] (mmol/d)	Urinary K (mmol/d)	Blood Pressure SBP/DBP[c] (mm Hg)
0.43 mmol/L	88 mmol/L	↓ 47/↓ 21 Also associated with weight loss
39	60	142[d]/92[d]
177	64	148[d]/98[d]
370	69	150[d]/96[d]
		156[d]/104[d]
		159[d]/105[d]
25	56	
122	60	↑ 9/↑ 6
		MAP
38	62	107[d]
334	67	115[e]
15	68	119[d]/84[d]
343	67	120[d]/84[d]
		MAP
SS *SR*	*SS* *SR*	*SS* *SR*
3.7 10.5	56 63	105[d] 110[d]
215 259.7	60 72	124[e] 114[e]
		MAP
21		92[d]
214		95[d]
		SS *SR*
54	68	127[d]/82[d] 132[d]/85[d]
217	60	151[e]/95[e] 138[d]/90[d]

continued

TABLE 6-13 Continued

References	Study Design[a]	Sodium (Na) Intake g/d (mmol/d)	Na/ Potassium (K) Ratio
Overlack et al., 1995	46 men and women with essential HT		
	2.9 g K (75 mmol)	0.46 (20)	0.27
	1-wk crossover	6.9 (300)	4
		0.46 (20)	0.27
		6.9 (300)	4
Feldman et al., 1996	5 adults		
	1 wk	0.46 (20)	
		5.5 (240)	
Mark et al., 1975	6 men with borderline HT	0.23 (10)	0.1
	3.9 g K (100 mmol)	9.4 (410)	4.1
	10 d		
Koolen and van Brummelen, 1984	20 men and women with essential HT	1.2 (50)	
	2 wk	6.9 (300)	
Sowers et al., 1988	11 HT African-American men and women	0.92 (40)	
	2 wk	4.1 (180)	
Del Rio and Rodriguez-Villamil, 1993	30 men and women with essential HT	≈0.8 (35)	
	2 wk	≈4.7 (204)	
Ferri et al., 1996	61 men with essential HT,	0.46 (20)	0.28
	2.7 g K (70 mmol)	3.2 (140)	2
	2 wk	7.4 (320)	4.6
Zemel et al., 1986	6 HT African-American men and women	1 (43)	
	2 wk	4 (174)	
Weir et al., 1995	22 men and women with essential HT	0.92 (40)	
	2 wk	4.6 (200)	
Johnson et al., 2001	15 elderly subjects ISH,	0.92 (40)	
	0.92 g/d (40 mmol/d)	2.1 (90)	
	Na diet + sodium dose	3.2 (140)	
	2 wk	5.5 (240)	
		7.8 (340)	

Urinary Na[b] (mmol/d)	Urinary K (mmol/d)	Blood Pressure SBP/DBP[c] (mm Hg)					
		MAP					
		SS		*SR*			
22		102		101			
267		112		102			
		< 45 yr		> 45 yr			
20		101[d]		103[d]			
265		100[d]		108[e]			
		MAP					
16		98[d]					
194		96[d]					
5	72	120[d]/73[d]					
310	89	133[e]/80[e]					
		SS		*SR*			
57	70	143/91		140/90			
270	73	164[d]/103[d]		139[e]/91[e]			
		MAP					
34		100[d]					
196		106[e]					
48	62	155[d]/95[d]					
199	58	156[d]/96[e]					
27	57	161[d]/104[d]					
124	53	161[d]/104[d]					
291	52	169[e]/108[e]					
		SBP					
43		134[d]					
215		138[d]					
		SS			*SR*		
100		*SBP*	*DBP*	*MAP*	*SBP*	*DBP*	*MAP*
236		↑ 8.7	↑ 6.8	↑ 7.4	↓ 4.3	↓ 4.1	↓ 3.8
68	27	161.5/81.1			↑ 9.0/↓ 0.3		
123	30	170.5/80.8			↑ 10.8/↑ 2.8		
180	30	172.3/83.9			↑ 14.9/↑ 3.1		
262	27	176.4/84.2			↑ 20.9/↑ 6.5		
373	28	182.4/87.6					

continued

TABLE 6-13 Continued

References	Study Design[a]	Sodium (Na) Intake g/d (mmol/d)	Na/ Potassium (K) Ratio
Johnson et al., 2001	8 elderly subjects with SDH, 0.92 g/d (40 mmol/d) Na diet + sodium dose 2 wk	0.92 (40) 2.1 (90) 3.2 (140) 5.5 (240) 7.8 (340)	
Parijs et al., 1973	22 men and women with HT 4-wk crossover		
MacGregor et al., 1982a	19 men and women with essential HT, Na-reduced diet + placebo or slow Na supplements 4 wk		
Watt et al., 1983	13 men and women with mild HT 4 wk		
Richards et al., 1984	12 men and women with mild essential HT 4 wk	1.8 (80) Na/ 2.3 g (60) K 4.1 (180) Na/ 2.3 g (60) K 4.1 (180) Na/ 7.8 g (200) K	1.3 3 0.9
Skrabal et al., 1984a	9 men and women with mild HT 4 wk	Low Na diet Normal diet	
MacGregor et al., 1989	20 men and women with mild HT 4 wk	1.1 (50) 2.3 (100) 4.6 (200)	
Benetos et al., 1992	20 men and women, reduced sodium diet + placebo or 61 mmol Na supplement 4 wk	+0 (0) 1.4 (61)	
Fotherby and Potter, 1993	17 elderly men and women, 80–100 mmol Na diet + placebo or 80 mmol Na supplement 5 wk	1.8 (80)–2.3 (100) 3.7 (160) 4.1(180)	

Urinary Na[b] (mmol/d)	Urinary K (mmol/d)	Blood Pressure SBP/DBP[c] (mm Hg)	
78	28	156.9/98.8	↑ 8.0/↓ 0.4
140	32	164.9/98.4	↑ 12.1/↑ 0.8
191	29	169.0/99.6	↑ 17.5/↑ 2.4
257	31	174.4/101.2	↑ 18.2/↑ 5.4
376	32	175.1/104.2	
93		138[d]/92[d]	
191		147[e]/98[e]	
86	59	144[d]/92[d]	
162	65	154[e]/97[e]	
59	47	139/87	
139	51	139/86	
100	60	145/91	
200	61	150/92	
205	190	148/91	
82		153/91	
214		147/91	
49	68	147[d]/91[d]	
108	75	155[e]/95[e]	
190	76	163[f]/100[f]	
85	63	143[d]/89[d]	
163	71	149[e]/93[e]	
95	65	171[d]/96[d]	
174	68	179[e]/96[d]	

continued

TABLE 6-13 Continued

References	Study Design[a]	Sodium (Na) Intake g/d (mmol/d)	Na/ Potassium (K) Ratio
Grobbee et al., 1987	40 young adult men and women with mildly elevated BP, no diet information, participants given placebo or 2.0 g (90 mmol) Na supplements 6 wk	+ 0 (0) + 2.1 (90) + 0/2.8 g (72) K supplement	
Cappuccio et al., 1997	29 elderly men 8 wk	≈1.9 (83) ≈3.9 (169)	
Weinberger et al., 1988	114 men and women with essential HT 30 wk		
Parallel studies			
Mulhauser et al., 1996	16 men and women high normal or mildly elevated BP 4 wk	2.1 (90) 4.4 (190)	
Dodson et al., 1989	34 men and women with mild HT, no diet information 3 mo		
Jula and Karanko, 1994	76 men and women with mild to moderate essential HT 12 mo		
Appel et al., 2001	681 men and women, 60–80 yr, on hypertensive medications 2–3 yr	Reduced sodium Usual lifestyle	

[a] HT = hypertension, ISH = isolated systolic hypertension, SDH = systolic diastolic hypertension.
[b] SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure.
[c] SS = salt sensitive, SR= salt resistant.
[d,e,f] Values with different superscripts differed significantly at $p < 0.05$.

Individual trials that tested three or more levels of sodium intake provide the best evidence to assess dose-response relationships between dietary sodium intake and blood pressure. Appendix I graphically displays results from each of the 10 trials available. Most used a randomized, crossover design. To assure fixed contrasts in sodium intake, most trials were feeding studies, which, because of logistic

Urinary Na[b] (mmol/d)	Urinary K (mmol/d)	Blood Pressure SBP/DBP[c] (mm Hg)
57	74	136/73
129	77	137/73
69	131	133/72
95	65	166/91
182	64	172/94
170 → 94	71 → 74	137/87 → 127/81
92	85	
199	94	↑ 4.9/↑ 5.3
137	64	↓ 11[d]/↓ 3.1[d]
181	68	↓ 4[e]/↓ 1[d]
109	84	134/89
166	83	135/92
144 → 99		↓ 4.3/↓ 2.0
145 → 140		

considerations, are necessarily brief in duration. No trial lasted for more than one month, and several lasted only a few days (see Appendix Table I-2). In most trials, the sample size was small, typically less than 20 persons. Hence there is a substantial risk of inadequate power and false negative results.

Of the available dose-response trials, the study by Luft and col-

leagues (1979b) tested the broadest range of sodium intake (0.23 to 34.5 g [10 to 1500 mmol]/day of sodium), albeit in just 14 individuals. Only two trials (Ferri et al., 1996; Sacks et al., 2001) enrolled over 50 persons, but the trial by Ferri and colleagues only enrolled hypertensive individuals. The trial by MacGregor and coworkers (1989) is a well-controlled trial that documented a direct, progressive relationship between sodium intake and blood pressure, but the trial enrolled only 20 individuals, all of whom were hypertensive. The trial by Johnson and colleagues (2001) tested increasing levels of sodium intake from baseline by giving four different levels of sodium chloride (range of total intake: 0.9 g [40 mmol]/day to 14.8 g [340 mmol]/day) in 46 individuals, 60 years of age and older; in each blood pressure stratum (nonhypertension, isolated systolic hypertension, and systolic-diastolic hypertension), there were significant, progressive, dose-response relationships between sodium intake and blood pressure.

A detailed overview of the trial by Sacks and colleagues (2001) is warranted in view of its size, duration, and other design features. This trial, termed the DASH-Sodium study, was a feeding study designed to test the effects on blood pressure of three levels of sodium intake (an average of 1.2, 2.3, and 3.5 g [50, 100, and 150 mmol]/day of sodium/2,100 kcal) separately in two distinct diets—the DASH (Dietary Approaches to Stop Hypertension) diet and a control diet (See Figure I-14 in Appendix I and corresponding Tables I-1a, b, c). The DASH diet is rich in fruits, vegetables, and low-fat dairy products and is reduced in saturated and total fat; accordingly, it is rich in potassium, magnesium, and calcium (corresponding to the 75th percentile of U.S. intake) (Appel et al., 1997). In contrast, the potassium, magnesium, and calcium levels of the control diet corresponded to the 25th percentile of U.S. intake, while its macronutrient profile and fiber content were similar to average U.S. consumption (Appel et al., 1997; Craddick et al., 2003) (see Table 6-9). A total of 412 participants enrolled; of these, 41 percent were hypertensive, 40 percent were white, and 57 percent were African American (Sacks et al., 2001).

Study participants were randomly assigned to the control or DASH diet, and, within their assigned diet, participants ate higher, intermediate, and lower sodium levels, each for 30 days in random order. By design, in the 2,100-kcal version of the diets, the higher sodium level was 3.5 g (150 mmol)/day of sodium. Thus the higher sodium level reflected typical U.S. adult consumption. The intermediate sodium level was 2.3 g (100 mmol)/day for the 2,100-kcal version, reflecting the upper limit of various recommendations

made in the United States (JNC, 1997). The lower level was 1.2 g (50 mmol)/day for 2,100 kcal (Sacks et al., 2001). The average achieved levels of sodium intake, as reflected by 24-hour urinary sodium excretion, were 142, 107, and 65 mmol/day, respectively, corresponding to approximate intakes of 3.3 g, 2.5 g, and 1.5 g, respectively (Sacks et al., 2001). Urinary potassium excretion averaged 79 and 41 mmol/24 hours on the DASH and control diets, respectively, and did not differ by level of sodium intake.

The main results of the DASH-Sodium trial (Sacks et al., 2001) are displayed in Appendix I—Figure I-14 and Tables I-la,b,c. On the control diet (Figure I-14 and Tables I-1a and 1c), reducing sodium intake from the higher (≈ 3.3 g) to the intermediate level (≈ 2.3 g) lowered systolic blood pressure by an average of 2.1 mm Hg ($p < 0.001$), while further lowering sodium intake from the intermediate to the lower level of sodium (1.2 g) led to an additional systolic blood pressure reduction of 4.6 mm Hg ($p < 0.001$). On the DASH diet (Figure I-14, Tables I-1a and 1b), corresponding reductions in systolic blood pressure were 1.3 ($p < 0.05$) and 1.7 mm Hg ($p < 0.01$), respectively. Hence decreasing sodium intake by approximately 0.92 g (40 mmol)/day caused a greater lowering of blood pressure when the starting sodium intake was at the intermediate level than when it was at a higher intake similar to the U.S. average.

The trial by Sacks and colleagues (2001) also provided an opportunity to assess the impact of sodium reduction in relevant subgroups (Vollmer et al., 2001; see Table 6-14). On the control diet, significant blood pressure reduction was evident in each subgroup. Reduced sodium intake led to greater systolic blood pressure reduction in individuals with hypertension compared with those classified as nonhypertensive, African Americans compared with non-African Americans, and older individuals (> 45 years old compared with those ≤ 45 years old). On the DASH diet, a qualitatively similar pattern was evident; however, some sub-group analyses did not achieve statistical significance, perhaps as a result of small sample size. Comparing the combined effect of the DASH diet with lower sodium with the control diet with higher sodium, the DASH diet with lower sodium reduced systolic blood pressure by 7.1 mm Hg in nonhypertensive persons and by 11.5 mm Hg in individuals with hypertension.

Other key findings emerged related to the dose-response relationship of sodium with blood pressure from the DASH-Sodium trial. First, the blood pressure response to sodium reduction was nonlinear, that is, there was a steeper decline in blood pressure when sodium was reduced from 2.3 g (100 mmol)/day to 1.2 g (50

TABLE 6-14 Effects on Systolic Blood Pressure of Reducing Dietary Sodium from the Higher to the Lower Levels in the Control Diet and the (DASH) Diet

Subgroup	n[a]	Effect of Lower Minus Higher Sodium in the Control Diet	Effect of Lower Minus Higher Sodium in the DASH[b] Diet
Hypertension status[c]			
Hypertensive	85/83	–8.3 (–10.0 to –6.6)[d]	–4.9 (–6.6 to –3.3)[e]
Nonhypertensive	123/121	–5.6 (–7.0 to –4.1)	–1.7 (–3.1 to –0.3)
Race			
African American	119/115	–8.0 (–9.4 to –6.5)[d]	–3.6 (–5.1 to –2.2)
Non-African American	89/89	–5.1 (–6.7 to –3.4)	–2.2 (–3.8 to –0.5)
Sex			
Female	123/111	–7.5 (–9.0 to –6.0)	–4.0 (–5.4 to –2.5)[d]
Male	85/93	–5.7 (–7.3 to –4.1)	–1.7 (–3.4 to 0.0)
Age			
> 45 yr	111/129	–7.5 (–8.9 to –6.1)[c]	–4.5 (–6.0 to –3.0)
≤ 45 yr	97/75	–5.3 (–7.0 to –3.5)	–1.4 (–2.9 to +0.2)
Body mass index			
Obese (≥ 30 kg/m^2)	78/82	–6.9 (–8.6 to –5.1)	–1.8 (–3.6 to 0.0)
Nonobese (< 30 kg/m^2)	130/122	–6.6 (–8.0 to –5.1)	–3.7 (–5.1 to –2.3)

[a] Number in DASH diet arm/number in control diet arm.
[b] DASH = Dietary Approaches to Stop Hypertension.
[c] Hypertensive patients had a SBP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg.
[d] $p < 0.05$ for comparing subgroup differences.
[e] $p < 0.01$ for comparing subgroup differences.

NOTE: Data expressed as mean (95% confidence interval) systolic blood pressure (SBP) mm Hg. All models included adjustment for baseline SBP, site, feeding cohort, and carryover effects. Unadjusted for other subgroups.

SOURCE: Adapted with permission from Vollmer et al. (2001). Copyright 2001 by American College of Physicians.

mmol)/day than when sodium is reduced from 3.4 g (150 mmol)/day to 2.3 g (100 mmol)/day (Sacks et al., 2001). Second, the DASH diet, compared with the control diet, blunted the effects of sodium on blood pressure, that is, over the same range of sodium intake, lowering sodium from 3.4 to 1.2 g (150 to 50 mmol)/day reduced blood pressure to a smaller extent on the DASH diet than on the control diet. Such findings, which may in part be a result of the higher potassium content of the DASH diet, are consistent with other studies that have documented that increased potassium

intake blunts the rise in blood pressure from sodium loading (Morris et al., 1999; see Chapter 5).

In addition to the 10 trials that directly tested three or more levels of sodium intake, the Trials of Hypertension Prevention–Phase 1 (Kumanyika et al., 1993) also assessed dose-response in post-hoc analyses based on achieved levels of sodium reduction (Figure 6-5). In this 18-month randomized trial in which 327 nonhypertensive individuals were assigned to a reduced sodium behavioral intervention and 417 individuals were assigned to a control group, there was a mean net reduction in urinary sodium excretion of 44 mmol (1.0 g)/day, as well as concurrent systolic/diastolic blood pressure reductions of 2.1/1.2 mm Hg. From the lowest quintile of sodium excretion at 18 months (< 65 mmol [1.5 g]/24 hours) to the highest (> 178 mmol [4.0 g]/24 hours), there were significant, direct dose-response relationships for both systolic and diastolic blood pressure. In analyses that corrected for intraperson variability in sodium excretion and blood pressure, the estimated average systolic and diastolic blood pressure reductions per 100 mmol (2.3 g)/

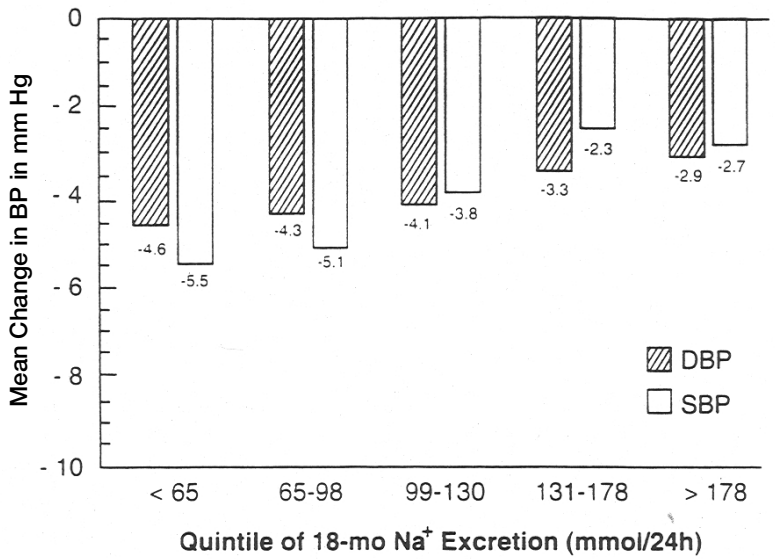

FIGURE 6-5 Mean change in diastolic blood pressure (DBP) and systolic blood pressure (SBP) from baseline for nonhypertensive individuals by quintile of urinary sodium excretion at 18 mo following a reduced sodium behavioral intervention program.
SOURCE: Kumanyika et al. (1993).

24-hour reduction in sodium excretion were 4.4/2.8 mm Hg (Cook et al., 1998).

Overall, available dose-response trials are consistent with a direct, progressive, dose-response relationship between sodium intake and blood pressure across a broad range of intake. This was clearly evident in the DASH-Sodium trial (Sacks et al., 2001), which was the largest trial and the study with the narrowest range of sodium intake (range: 1.2 g to 3.4 g [50 to 150 mmol]/day). A progressive relationship was also apparent in two smaller studies that tested four or more sodium levels across a broader range of sodium intake (range: 0.23 to 34.5 g [10 mmol to 1,500 mmol]/day [Luft et al., 1979b]; range: 0.92 to 7.82 g [40 to 340 mmol]/day [Johnson et al., 2001]). No trial tested multiple sodium levels below 2.3 g (100 mmol)/day. However, observational analyses of the four isolated populations in the Intersalt study suggest a progressive relationship for systolic blood pressure at urinary sodium levels between less than 0.02 g (1 mmol)/day in the Yanomamo Indians and 1.2 g (51 mmol)/day in Kenyans (Mancilha-Carvalho and Souza e Silva, 2003).

Effects of Sodium Intake on Blood Pressure: Evidence from Meta-Analyses of Intervention Studies. Several meta-analyses of clinical trials have been conducted to assess the effects of sodium intake on blood pressure (Table 6-15). Typically, these studies estimate the ratio of the average change in blood pressure to observed average change in sodium intake. However, such ratios cannot be used to assess dose response unless the relationship is linear. For sodium, available evidence indicates that it is nonlinear (Sacks et al., 2001).

The earliest meta-analyses aggregated data across a wide range of study designs, from very brief feeding studies lasting a few days to long-term behavioral intervention studies lasting a year or more. These meta-analyses have provided consistent evidence that a reduced sodium intake lowers systolic and diastolic blood pressure in hypertensive individuals. However, the extent of blood pressure reduction in nonhypertensive individuals is less consistent. In the largest of these meta-analyses (Cutler et al., 1997; Graudal et al., 1998; Midgley et al., 1996), the average decrease in systolic/diastolic blood pressure per 100 mmol (2.3 g) reduction in daily sodium excretion in hypertensive individuals was 5.8/2.5, 3.3/1.6, and 3.7/0.9 mm Hg, respectively. The corresponding reductions in systolic/diastolic blood pressures in nonhypertensive persons were 2.3/1.4, 0.8/0.2, and 1.0/0.1 mm Hg, respectively.

In view of the substantial heterogeneity in study design, subsequent meta-analyses focused on distinct types of trials or popula-

tions. One meta-analysis focused on trials conducted in older-aged persons (mean age close to 60 years) (Alam and Johnson, 1999). In this meta-analysis, which included both nonhypertensive and hypertensive persons, sodium reduction significantly lowered systolic and diastolic blood pressure by 5.58 and 3.5 mm Hg, respectively. The effect was more pronounced in trials that exclusively enrolled individuals older than age 60.

A meta-analysis was conducted to assess the effect of modest sodium reduction to levels that would be relevant to public health decision-making (He and MacGregor, 2002). Trials of brief duration and those with extremely low sodium intakes were excluded. All of the included trials lasted 4 or more weeks, and many were controlled feedings studies. In aggregate, a median sodium reduction of approximately 1.7 g (75 mmol)/day led to significant reductions in systolic and diastolic blood pressure of 2.0 and 1.0 mm Hg in non-hypertensive individuals (11 trials) and 5.0 and 2.7 mg Hg in hypertensive patients (17 trials) (He and MacGregor, 2002).

Another meta-analysis assessed the long-term effects of advice to reduce sodium intake (Hooper et al., 2002). This meta-analysis has also been published as a Cochrane Review (Hooper et al., 2003). Most included trials used intensive behavioral interventions in free-living individuals. By design, the authors included only trials that lasted 6 or more months. The total duration of the trials ranged from 6 months to 7 years. Net reduction in urinary sodium excretion as the result of the behavioral interventions was 35.5 mmol (0.8 g)/24 hours, roughly half the net reduction observed in the meta-analysis by He and MacGregor (2002). On average, systolic and diastolic blood pressure reductions were 1.1 ($p = 0.002$) and 0.6 ($p = 0.19$) mm Hg, respectively. This meta-analysis documents the difficulties of sustaining a reduced sodium intake in free-living persons over the long-term. Because of the limited net reduction in sodium intake as evidenced by attained urinary sodium excretion, the efficacy of sodium reduction as a means to lower blood pressure cannot be assessed from this analysis.

Primary Prevention of Hypertension. Almost 50 million adult Americans, or approximately 25 percent of the U.S. adult population, have hypertension, defined as a systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, and/or current use of antihypertension medication (Burt et al., 1995; Hajjar and Kotchen, 2003). In Canada, approximately 27 percent of adults 35 to 64 years old have hypertension (Wolf-Maier et al., 2003). Above-normal blood pressure in the nonhypertensive range, that is, systolic blood

TABLE 6-15 Meta-analyses of Studies on Sodium/Salt Intake and Blood Pressure

Reference	Trial Selection	Number of Studies
Cutler et al., 1991	Randomized trials	23 trials representing 1,536 subjects
Law et al., 1991b	Nonrandomized and randomized control trials	78 trials, including 33 trials lasting 5 wk or longer
Midgley et al., 1996	Randomized trial with control and dietary Na intervention; Na intake monitored by urinary Na excretion	28 hypertensive trials and 28 nonhypertensive trials representing 3,505 subjects
Brunner et al., 1997	Randomized, controlled trials of at least 3 mo duration	17 trials representing 6,893 subjects
Cutler et al., 1997	Randomized controlled trials (crossover and parallel)	32 trials representing 2,635 subjects
Graudal et al., 1998	Randomization of a low- and high-Na diet; Na excretion was measured	58 hypertensive and 56 nonhypertensive trials representing 4,742 subjects
Alam and Johnson, 1999	Randomized, controlled studies of chronic Na ingestion in elderly (mean age close to or greater than 60 yr)	11 trials representing 485 subjects
He and MacGregor, 2002	Randomized trials of modest Na reduction that lasted 4 or more wk	17 hypertensive trials and 11 nonhypertensive trials representing 954 subjects
Hooper et al., 2002	Randomized trials of behavioral interventions to reduce Na intake that lasted at least 6 mo	3 nonhypertensive trials, 5 hypertensive trials (untreated), and 3 treated hypertensive trials representing 3,514 subjects
Geleijnse et al., 2003	Randomized trials with a minimum duration of 2 wk	19 nonhypertensive trials, 28 hypertensive trials

[a] SBP = systolic blood pressure, DBP = diastolic blood pressure, NT = nonhypertensive, HT = hypertensive.

Results[a]
Decreased BP by 1.7 ± 1.0; 1.0 ± 0.7 mm Hg (systolic and diastolic, respectively, with 95% confidence limits) in NT individuals and 4.9 ± 1.3; 2.6 ± 0.8 mm Hg in HT subjects
Reducing daily sodium (Na) intake by 1.2 g (50 mmol) in individuals aged 50–59 yr lowered SBP by an average of 5 mm Hg, and by 7 mm Hg in individuals with hypertension (SBP ≥170 mm Hg); a reduction in DBP was about half of the values above
For NT individuals, 2.3 g/d (100 mmol/d) reduction in daily Na excretion resulted in 1.0 mm Hg and 0.1 mm Hg reduction in SBP and DBP, respectively The decrease in BP for a 100 mmol/d (2.3 g/d) reduction in daily Na excretion was 3.7 mm Hg for SBP and 0.9 mm Hg for DBP for HT individuals
A decrease of 45 mmol/d (1.0 g/d) of urinary Na resulted in a decrease in SBP and DBP by 1.9 and 1.2 mm Hg, respectively
Lowering Na resulted in a reduction in SBP and DBP of: (1) 1.9 and 1.1 mm Hg respectively in NT subjects; (2) 4.8 and 2.5 mm Hg respectively in HT subjects
A reduction in urinary Na excretion was related to decreases in SBP and DBP of: (1) 1.2 and 0.26 mm Hg, respectively, in NT individuals; (2) 3.9 and 1.9 mm Hg respectively in HT patients
A high sodium chloride diet significantly increased SBP and DBP by 5.58 and 3.5 mm Hg, respectively
A median reduction of urinary Na of 1.7 g/d (74 mmol/d) in NT and of 1.8 g/d (78 mmol/d) in HT led to decreased SBP and DBP of 2.0 and 0.97 mm Hg for NT and 4.96 and 2.7 mm Hg for HT
SBP and DBP were reduced by 1.1 and 0.6 mm Hg with a reduced urinary Na of 35 mmol/d (0.8 g/d) Degree of reduction in Na intake was not related to change in BP
Median reduction of 77 mmol (1.8 g)/d reduced SBP by 4.1 mm Hg and DBP by 2.5 mm Hg SBP/DBP reduction in HT and NT were 5.2/3.7 mm Hg and 1.3/1.1 mm Hg, respectively

pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 90 mm Hg, has been found to confer excess cardiovascular disease risk (see Figure 6-4). It has been estimated that almost one-third of blood pressure-related deaths from coronary heart disease are estimated to occur in individuals with blood pressure in this range (Stamler et al., 1993).

The prevalence of hypertension rises progressively with age, such that more than half of all Americans 60 years of age or older have hypertension (Hajjar and Kotchen, 2003). Among nonhypertensive adults, the estimated lifetime risk of developing hypertension is 0.9 (Vasan et al., 2002). The rise in blood pressure with age, while commonplace in Western countries, is not universal, as there are non-Western populations, as well as some Western populations (e.g., strict vegetarians), in which the rise in blood pressure with age is minimal or nonexistent (Rose et al., 1988; Sacks et al., 1974). In ecologic observational studies, a reduced intake of sodium and an increased intake of potassium have been associated with a blunted age-related rise in blood pressure (Rose et al., 1988).

Primary prevention of hypertension has been suggested as an opportunity to interrupt and prevent the continuing and costly cycle of managing hypertension and its consequences (NHBPEP, 1993; Whelton et al., 2002). Hypertension can be prevented by complementary application of strategies aimed at achieving a downward shift in the distribution of blood pressure in the general population (population-based strategy) and more intensive targeted strategies aimed at achieving a greater reduction in blood pressure in individuals and groups at greater risk for high blood pressure (intensive targeted strategy) (Whelton et al., 2002). Because the health benefits of a population strategy are applied to large numbers, even small downward shifts in the distribution of blood pressure can be expected to result in a substantial reduction in the burden of illness in the population being targeted (Rose, 1985; Whelton et al., 2002). For example, a downward shift in the population distribution of systolic blood pressure by 2 mm Hg would be expected to result in an annual reduction of 6 percent in mortality from stroke and 4 percent from coronary heart disease (Stamler, 1991). The corresponding estimates would be 8 and 5 percent for a 3-mm Hg downward shift in the population distribution of systolic blood pressure, and 14 and 9 percent for a 5 mm Hg shift (Stamler, 1991). Sodium reduction is one of several nutritional therapies that have been proposed as a means to reduce blood pressure and thereby affect a downward shift of blood pressure in the population (Chobanian et al., 2003). Weight control, moderation of alcohol intake, and con-

sumption of the DASH diet, which is rich in potassium and other minerals, have also been included as part of a comprehensive nutritional approach to reduce blood pressure.

To date, three trials have explored the effects of a reduced sodium intake as a means to prevent hypertension (Hypertension Prevention Trial [HPT], Trial of Hypertension Prevention Phase I [TOHP1], and Phase II [TOHP2]). HPT and TOHP1 were pilot studies, conducted to inform the design of TOHP2. Each study was a controlled trial in which there was a behavioral intervention that focused exclusively on reducing sodium intake. In HPT and TOHP2, there were also groups that simultaneously implemented other interventions: increased potassium intake in HPT and weight loss in TOHP2. As shown in Table 6-16, net reductions in urinary sodium excretion on the sodium reduction arm were modest in the three studies, ranging from 13 to 57 mmol/day, at the end of follow-up. In this setting, the relative risk of incident hypertension associated with a reduced sodium intervention that did not include any other lifestyle change ranged from 0.69 to 0.82.

Results from TOHP2 are especially relevant because this trial was designed to test the effects of a reduced dietary sodium intervention as a means to prevent hypertension. TOHP2 was a randomized, controlled 2×2 factorial trial that tested the effects of three behavioral interventions (sodium reduction, weight loss, or combined weight loss and sodium reduction) on blood pressure and incident hypertension over 3 to 4 years of follow-up in overweight individuals aged 30 to 54 years with an initial diastolic blood pressure of 83 to 89 mm Hg and a systolic blood pressure < 140 mm Hg. At 6 months, the height of intervention adherence, the incidence of hypertension was lowest in the combined group (2.7 percent), intermediate in the weight loss (4.2 percent) and sodium reduction (4.5 percent) groups, and highest in the control group (7.3 percent). At 18 months, the pattern persisted. By the end of follow-up, the incidence of hypertension was 18 to 22 percent less in each behavioral intervention group ($p < 0.05$ compared with control), but not different when compared with each other. Results of this trial indicate that behavioral interventions can prevent hypertension over the long-term. Also, the pattern of incident hypertension at 6 and 18 months suggests that the effects of weight loss and reduced sodium intake, under optimal conditions of adherence, may be additive.

It is important to note that a major barrier to the achievement of greater reductions in blood pressure and reductions in the associated cardiovascular disease complications is reliance on behavioral interventions to reduce dietary intake of sodium. In contrast to the

TABLE 6-16 Effect of Behavioral Interventions Designed to Test the Effect of Sodium Reduction on Preventing Hypertension

Study	*n*	Duration (mo)	Baseline Sodium (Na) Excretion (mmol/d)
Hypertension Prevention Trial (Hypertension Prevention Trial Research Group, 1990)			
Control (overweight stratum)	126	36	174
Sodium reduction alone (overweight stratum)	126	36	171
Control (nonoverweight stratum)	196		165
Sodium reduction alone (nonoverweight stratum)	196	36	163
Sodium reduction with increased potassium (nonoverweight stratum)	196		160
Trials of Hypertension Prevention-Phase I (TOHP Collaborative Research Group, 1992a, 1992b)			
Control	417		156
Sodium reduction alone	327	18	154
Trials of Hypertension Prevention—Phase II (TOHP Collaborative Research Group, 1997)			
Control	596	36–48	188
Sodium reduction alone	594		186
Weight loss alone	595		181
Sodium reduction with weight loss	597		179

short-term (3-day) feeding trials that could achieve contrasts in sodium intake of nearly 34.3 g (1490 mmol)/day (Luft et al., 1979a, 1979b), the maximum contrast in the primary prevention trials was 1.3 g (57 mmol)/day in TOHP1 (see Table 6-16). Greater and more sustainable reductions in sodium intake could be expected from a diminution in the amount of sodium added during food processing (approximately 80 percent of sodium consumed in westernized countries is derived from food products) rather than via reduction in sodium used during cooking or at the table (Sanchez-

Net Achieved Na Excretion (mmol/d)		Net Na Excretion Reduction (mmol/d)			
6 mo	End of Follow-up	6 mo	End of Follow-up	Relative Risk of Hypertension Relative to Control Group	
157	183			1.00	
141	160	–19	–13	0.69 ($p = 0.066$, comparing all groups in overweight strata)	
150	165				
127	147	–16	–21	0.73 ($p = 0.01$, comparing all groups in nonoverweight strata)	
117	138	–22	–29	0.65	
159	145				
98	99	–72	–57	0.76 (95% confidence interval: 0.49–1.18)	
				6 mo Results	*End of Study Results*
177				1.00	1.00
108	135	–50	–40	0.61 ($p = 0.04$)	0.82 ($p = 0.05$)
163	172	9	2	0.58 ($p = 0.02$)	0.79 ($p = 0.02$)
115	145	–37	–24	0.37 ($p < 0.001$)	0.78 ($p = 0.01$)

Castillo, 1987). Given the current market availability of lower-sodium food products, careful selection is necessary to lower sodium intake.

Stroke and Coronary Heart Disease

A strong positive association between salt intake and cardiovascular disease, especially stroke, has been documented in a variety of animal models (Chen et al., 1997; Coyle, 1988). In humans, a simi-

lar association between salt intake and evidence of stroke has been noted in most cross-sectional studies (Ikeda et al., 1986; Perry and Beevers, 1992; Sasaki et al., 1995; Yamori et al., 1994; Yang et al., 1997) (see Table 6-17). In Japan, a public health campaign to reduce average dietary sodium intake was associated with a significant reduction in the prevalence of hypertension and hemorrhagic stroke, a major cause of death in this population before sodium intake decreased (Yamori and Horie, 1994). Increased sodium intake has also been associated with increased left ventricular mass, a subclinical form of cardiovascular disease (Liebson et al., 1993).

Results of prospective studies have been less consistent, primarily because of methodological limitations. Early reports did not find a significant relationship between dietary sodium intake and risk of stroke (Kagan et al., 1985), but statistical power in these studies was limited. To a large extent, inadequate power reflects the imprecision associated with most approaches to the measurement of habitual sodium intake. In particular, a high ratio of intraindividual to interindividual variation in sodium intake, which is commonplace in westernized populations (Liu et al., 1979), tends to diminish statistical power and the ability to detect even clinically important associations. Hence, large cohorts are needed in order to yield meaningful results.

Two epidemiological studies published by Alderman and coworkers (1995, 1998b) have been interpreted as providing evidence that low sodium diets have an adverse effect on human health. In the first of these studies, Alderman and colleagues (1995) reported the presence of a significant inverse association between urinary sodium excretion and incident myocardial infarction in a prospective cohort study conducted in 2,937 treated hypertensive patients. As indicated in an accompanying editorial and in subsequent communications, however, the assessment of sodium intake and imprecision in the measurement of potentially confounding variables might have contributed to the occurrence of this unexpected finding (Cook et al., 1995b; MacGregor, 1996).

Urinary sodium excretion as obtained and reported in this study did not represent habitual dietary sodium intake. First, participants were advised to reduce their sodium intake prior to the collection of urine. After 5 days on a reduced sodium intake, urinary sodium excretion was measured. Second, there is evidence of differential noncompliance in that creatinine excretion in the lowest quintile of sodium excretion was markedly and unexpectedly lower, thus indicating a high probability of incomplete urine col-

lections. Hence, the interpretation of the urinary sodium data in this study is uncertain.

Other findings from this study complicate its interpretation. The relationship between urinary sodium excretion and myocardial infarction was inverse in men, but direct in women. Plasma renin concentrations did not increase proportionately to the reduction in sodium excretion as might be anticipated. Also, the study was conducted in hypertensive patients who were enrolled in a work-site treatment program, making it difficult to know whether the findings would have general application. While the authors have responded to these concerns (Alderman and Laragh, 1996), interpretation of the findings from this study remains difficult.

In a second study, Alderman and colleagues (1998b) took advantage of the large sample size, nutrient intake database, and prolonged follow-up of participants in the National Health and Nutrition Examination Survey I (NHANES I) Epidemiologic Follow-up Study to examine the relationship between sodium intake as obtained from self-reported dietary information and the subsequent risk of cardiovascular disease. They identified an inverse relationship between sodium intake and mortality from cardiovascular diseases ($p = 0.09$) and all causes ($p < 0.007$), but a positive relationship between sodium:calorie ratio and mortality from cardiovascular diseases ($p = 0.006$) and all causes ($p = 0.004$).

In addition to the inconsistency between the direction of the association with the two methods of estimating sodium intake (directly, or as adjusted based on estimated energy intake), several methodological concerns make it difficult to interpret the findings. Participants with a baseline history of cardiovascular diseases were included in the main analysis, albeit such participants might be expected to have changed their dietary intake of sodium prior to dietary assessment. Acute rheumatic fever, chronic rheumatic heart disease, and diseases of the pulmonary circulation were included as cardiovascular mortality outcomes, although the biological basis for a relationship between sodium intake and these diseases is not obvious. As in the prior report by Alderman and colleagues, there is again evidence of differential completeness of dietary data. Of greatest concern is the fact that the highly correlated variables of sodium intake, caloric intake, and sodium:calorie ratio were simultaneously included in the same multivariate model. The authors have responded to these criticisms (Alderman et al., 1998a).

In contrast to the studies reported by Alderman and colleagues, other prospective studies either did not identify an association between sodium intake and cardiovascular disease or identified a sig-

TABLE 6-17 Observational Studies of Sodium Intake and Risk of Stroke or Coronary Heart Disease (CHD)

Reference	Study Design	Sodium (Na) Intake[a] (g/d)
Stroke		
Kagan et al., 1985	Prospective cohort, 10-yr follow-up, *n* = 7,895 Japanese men, multivariate analysis	
Perry and Beevers, 1992	Intersalt study, cross-sectional, *n* = 3,942 men and women	
Yamori et al., 1994	CARDIAC Study, cross-sectional, 14 countries	
Sasaki et al., 1995	Cross-sectional data collected from 24 published studies	
Alderman et al., 1997	Prospective cohort, 3.8-yr follow-up, 2,937 men and women	Urinary Na (mmol/24 h) *Men* Q1 < 89 Q2 89–126 Q3 127–174 Q4 > 174 *Women* Q1 < 66 Q2 66–97 Q3 98–138 Q4 > 138
Yang et al., 1997	Cross-sectional, 13 target populations in China	
He et al., 1999	NHANES I, prospective cohort, *n* = 9,485, multivariate analysis	*Nonoverweight* Q1 1.97 Q2 3.0 Q3 3.87 Q4 5.6 *Overweight* Q1 1.8 Q2 2.7 Q3 3.5 Q4 5.1

Results[b]	Other Results and Comments
No association was found between urinary Na and incidence of stroke	
Significant positive association between Na excretion and stroke mortality ($p < 0.008$)	
Significant positive correlation between Na excretion and stroke mortality in men ($p < 0.01$)	
Positive correlation between urinary Na and rate of stroke mortality ($p < 0.01$ to $p < 0.001$)	
RR for Stroke 1.0	
1.6	
1.0	
0.5	
Positive correlation between Na intake and stroke mortality ($p = 0.029$)	
RR for Stroke 1.0 1.05 0.93 0.95 p trend = 0.47	*RR for CHD* 1.0 1.34 1.05 1.06 p trend = 0.77
1.0 1.28 1.64 1.51 p trend = 0.02	1.0 0.96 1.0 0.97 p trend = 0.86
Among overweight individuals, a 2.3-g (100 mmol/d) increase in Na was associated with a 32% increase in stroke incidence (and 89% increase in stroke mortality)	

continued

TABLE 6-17 Continued

Reference	Study Design	Sodium (Na) Intake[a] (g/d)
Coronary heart disease		
Ikeda et al., 1986	Cross-sectional, 1,310 men and women from 49 regions in Japan	
Alderman et al., 1997	Prospective cohort, 3.8-yr follow-up, 2,937 men and women	Urinary Na (mmol/24 h) *Men* Q1 < 89 Q2 89–126 Q3 127–174 Q4 > 174 *Women* Q1 < 66 Q2 66–97 Q3 98–138 Q4 > 139
Tunstall-Pedoe et al., 1997	Scottish Heart Health Study, prospective, *n* = 11,629 men and women, 7.6 yr of follow-up	Urinary Na (mmol/L/d) *Men* Q1 46.8 Q2 129.6 Q3 168.4 Q4 204.1 Q5 251.3 *Women* Q1 37.8 Q2 98.0 Q3 123.4 Q4 149.0 Q5 187.3
Alderman et al., 1998b	NHANES I prospective cohort, 17- to 21-yr follow-up, *n* = 11,346 men and women, not energy adjusted	Q1 1.44 Q2 2.13 Q3 2.66 Q4 3.83
Tuomilehto et al., 2001	Prospective cohort, 2,436 men and women	

[a] Q = quartile or quintile.
[b] RR = relative risk.
[c] CHD = coronary heart disease.

Results[b,c]	Other Results and Comments
There was a significant positive correlation between Na intake and mortality from CVD, cerebral infarction, and subarachnoid hemorrhage; Also a positive association between Na and Na:Potsssium ratio and ischemic heart disease mortality	
RR for CVD 1.0	
2.7	
1.0	
0.4	
RR for CHD 1 1.18 1.11 1.26 1.23	Over 7.6 yr of follow-up, there was a significant positive association between urinary Na and incidence of CHD in women only ($0.01 \leq p < 0.05$)
1 0.93 0.97 1.09 1.76	
CVD mortality/100 person yr 11.8 10.0 (estimated from graph) 10.4 (estimated from graph) 9.6	Significant inverse association ($p < 0.0019$)
Adjusted hazard ratios for CHD, CVD, and all-cause mortality in men and women associated with a 100 mmol/d increase in urinary Na excretion were 1.56, 1.36, and 1.22, respectively	Significant, direct relationships of urinary Na excretion with cardiovascular outcomes in overweight persons; nonsignificant in nonoverweight individuals

nificant direct association. In analyses of the Multiple Risk Factor Intervention Trial (MRFIT), there were no significant relationships between sodium intake (as assessed by multiple 24-hour dietary recalls) and mortality from total cardiovascular disease, coronary heart disease, or stroke (Cohen et al., 1999). During the initial 7.6 years of follow-up in the Scottish Heart Health Study, there was no significant relationship between sodium intake and coronary heart disease events in men, but a significant positive relationship in women (Tunstall-Pedoe et al., 1997); these analyses were only adjusted for age.

Several epidemiological and clinical studies have suggested that overweight persons may be more sensitive to the effects of sodium on blood pressure (Altschul et al., 1981; He et al., 1994; Rocchini et al., 1989). In this setting, two prospective studies examined the effects of sodium intake on cardiovascular outcomes in analyses stratified by overweight status (He et al., 1999; Tuomilehto et al., 2001). He and colleagues (1999) analyzed the relationship between self-reported sodium intake and risk of cardiovascular disease in the NHANES I Epidemiologic Follow-up Study. In contrast to previous analyses using the same database reported by Alderman and colleagues (1998b), He and colleagues (1999) excluded those individuals with a history of cardiovascular disease or its treatment and those who intentionally consumed a low-salt diet. Of the 9,485 remaining participants (113,467 person-years of follow-up), 2,688 were overweight (cut-off for overweight was Body Mass Index [BMI] > 27.8 kg/m^2 for men and 27.3 kg/m^2 for women). As estimated from a single 24-hour dietary recall that did not include discretionary salt use, baseline median sodium intake in the quintiles (based on the sodium-energy ratio) ranged from 1.2 to 3.3 g (50.5 to 142.5 mmol)/day in the quintiles for the nonoverweight adults, and 1.0 to 3.0 g (45.5 to 129.7 mmol)/day in the quintiles of overweight participants. In the overweight stratum, there were consistent and highly significant positive relationships between baseline dietary intake of sodium and risk of stroke, cardiovascular disease, and total mortality. In multivariate analyses, a 2.3 g (100 mmol)/day higher intake of sodium was associated with a 32 percent increase (relative risk [RR] = 1.32; 95 percent confidence interval [CI] = 1.07–1.64) in stroke incidence, an 89 percent increase (RR = 1.89; 95 percent CI = 1.31–2.74) in stroke mortality, a 44 percent increase (RR = 1.44; 95 percent CI = 1.14–1.81) in coronary heart disease mortality, a 61 percent increase (RR = 1.61; 95 percent CI = 1.32–1.96) in cardiovascular disease mortality, and a 39 percent increase (RR = 1.39; 95 percent CI = 1.23–1.58) in mortality from

all causes in overweight persons. Dietary sodium intake was not significantly associated with nonfatal coronary heart disease in overweight participants or with risk of cardiovascular disease in participants with normal weight. In a subsequent analysis of the NHANES database by He and colleagues (2002), dietary sodium intake was a significant, independent risk factor for congestive heart failure in overweight individuals.

In a prospective study conducted in 1,173 Finnish men and 1,263 women aged 25 to 64 years, the adjusted hazard ratios for coronary heart disease, cardiovascular disease, and all-cause mortality, associated with a 100 mmol (2.3 g) higher level of 24-hour urinary sodium excretion, were 1.56 (95 percent CI = 1.15–2.12), 1.36 (1.05–1.76) and 1.22 (1.02–1.47), respectively (Tuomilehto et al., 2001). There was an interaction between sodium excretion and BMI for cardiovascular and total mortality, with sodium intake being a significant predictor of cardiovaslcular disease and total mortality in men who were overweight (RR = 1.44 and 1.56, respectively), and a nonsignificant predictor of both outcomes in the normal-weight subset (RR = 1.23 and 0.98, respectively).

Overall, observational studies, particularly ecological studies, suggest that higher levels of sodium intake increase the risk of cardiovascular disease, especially stroke. Of the available prospective observational studies, those with the most rigorous methods have likewise documented a positive relationship, which was evident in overweight individuals. Still, conclusive evidence of a causal relationship typically depends on results of appropriately designed clinical trials that test the effects of sodium reduction on clinical cardiovascular outcomes. While some persons have advocated such a trial, the feasibility of such an endeavor is uncertain, especially in view of the well-documented difficulties in establishing and maintaining a large contrast in sodium intake over the long-term (Table 6-16).

Left Ventricular Mass

Increased left ventricular mass or wall thickness (left ventricular hypertrophy) is a subclinical form of cardiovascular disease that is a powerful predictor of cardiovascular morbidity and mortality, including myocardial infarction, stroke, congestive heart failure, and sudden death (Bikkina et al., 1994; Casale et al., 1986; Koren et al., 1991; Levy et al., 1990; Messerli and Soria, 1994). Echocardiography is a sensitive diagnostic technique that is used to estimate left ventricular mass. In the Framingham Heart Study, elevated left ventricular mass as measured by echocardiography was associated

with an increased incidence of cardiovascular disease in both men and women, after adjustment for traditional cardiovascular risk factors (Levy et al., 1990). The 5-year mortality for electrocardiographic left ventricular hypertrophy was 33 percent for men and 21 percent for women (Kannel, 1991).

Increased left ventricular mass is thought to be, in part, a structural adaptation of the heart as a compensatory mechanism for increased blood pressure and wall stress. Increased blood pressure is one of the strongest correlates of left ventricular mass (Liebson et al., 1993). Not surprisingly, factors associated with elevated blood pressure are also associated with increased left ventricular mass, including obesity (de Simone et al., 1994; Schmieder and Messerli, 1993), aging (Alderman et al., 1995; Ghali et al., 1997), African-American race (Harshfield et al., 1992), and, as discussed subsequently, sodium intake.

Several cross-sectional studies have examined the relationship between sodium intake, typically as measured by urinary sodium excretion, and left ventricular mass or hypertrophy, as measured by echocardiography. Other cross-sectional studies have documented associations between sodium intake and cardiac function, such as impaired diastolic filling (Langenfeld et al., 1998).

Most reports used correlation or regression analyses and did not report left ventricular mass by level of urinary sodium excretion. Available studies predominantly enrolled hypertensive adults, but some enrolled nonhypertensive individuals (du Cailar et al., 2002; Kupari et al., 1994) or children (Daniels et al., 1990; Harshfield et al., 1994). With the exception of the study by Alderman and colleagues, which assessed left ventricular hypertrophy by electrocardiography and did not detect an association, each study documented a statistically significant, positive relationship between urinary sodium excretion and left ventricular mass (Daniels et al., 1990; du Cailar et al., 1989, 1992, 2002; Gerdts et al., 1996; Kupari et al., 1994; Langenfeld et al., 1998; Liebson et al., 1993; Schmieder et al., 1988, 1990, 1996). Figure 6-6 displays results from the report of Schmieder and coworkers (1988), who were the first to report an association between sodium intake and left ventricular hypertrophy. The only two studies that reported left ventricular mass by level of dietary sodium are included in Table 6-18.

In most studies, the association between urinary sodium excretion and left ventricular mass persisted after adjustment for other determinants of left ventricular mass, including blood pressure (du Cailar et al., 2002; Liebson et al., 1993). Such findings, in conjunction with animal studies, raise the possibility that sodium may have a

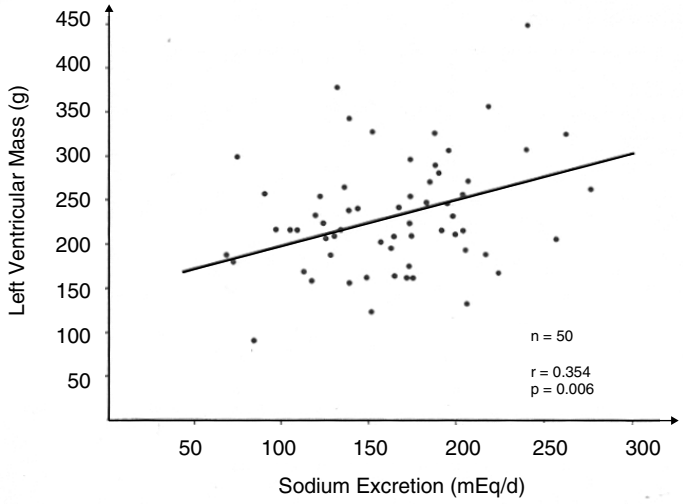

FIGURE 6-6 Relationship of dietary salt intake to left ventricular mass. Reprinted with permission from Schmieder et al. (1988). Copyright 1988 by Lippincott, Williams, and Wilkins.

trophic effect—a direct effect on left ventricular mass apart from indirect effects mediated through blood pressure. Potential mechanistic pathways by which sodium might exert a direct effect on left ventricular mass include the renin-angiotensin system, the sympathetic nervous system, and fluid-volume homeostasis (Beil et al., 1994).

Four clinical trials assessed the effects of a reduced sodium intake on left ventricular mass in hypertensive individuals. In three trials, the comparison group received antihypertensive drug therapy (Fagerberg et al., 1991; Ferrara et al., 1984; Liebson et al., 1995). In two of these trials, the nonpharmacological intervention included weight loss, as well as sodium reduction (Fagerberg et al., 1991; Liebson et al., 1995). In each of the three trials with an active drug treatment comparison group, reductions in left ventricular mass were similar in the pharmacological and nonpharmacological intervention groups. In view of the well-documented effects of antihypertensive drug therapy on left ventricular mass in controlled trials (Klingbeil et al., 2003), these three studies suggest that the nonpharmacological interventions are likewise effective. However, because two of the trials included weight loss in the nonpharmacological interventions, one cannot attribute the effects to a reduced sodium intake.

TABLE 6-18 Observational Studies Relating Left Ventricular Mass or Left Ventricular Hypertrophy to Sodium Intake

Reference	Study Design		Urinary Sodium[a] g/d	Urinary Sodium[a] mmol/d	% LVH by Electrocardiogram[b]
Alderman et al., 1997	Cross-sectional analyses of baseline data, n = 1,900 men and 1,037 women	*Men*			
		Q1	< 2	< 89	12
		Q2	2–2.9	89–126	11
		Q3	3–4	127–174	9
		Q4	≥ 4	≥ 175	11
					p = 0.68
		Women			
		Q1	< 1.5	< 66	5
		Q2	1.5–2.2	66–97	4
		Q3	2.2–3.2	98–138	4
		Q4	> 3.2	> 138	5
					p = 0.84
du Cailar et al., 2002	Cross-sectional, n = 839 men and women, multivariate analysis	*Men*			*LVM* ($g/m^{2.7}$)
		Q1	0.74–2.5	32–110	46
		Q2	2.6–3.3	111–142	47
		Q3	3.3–3.9	143–172	48
		Q4	4.0–5.1	173–220	50
		Q5	5.1–9.5	221–415	55
					p = 0.007
		Women			
		Q1	0.41–1.9	18–86	38
		Q2	2.0–2.5	87–110	42
		Q3	2.6–3.0	111–131	44
		Q4	3.0–3.9	132–168	44
		Q5	3.9–7.1	169–310	46
					p = 0.006

[a] Q = quartile or quintile.
[b] LVH = left ventricular hypertrophy, LVM = left ventricular mass.
NOTE: Sodium intake estimated to be approximately equal to urinary excretion.

Only one trial tested a reduced sodium intervention and compared its effects with that of a nonintervention control group (Jula and Karanko, 1994). In this randomized trial that enrolled 76 hypertensive individuals, mean urinary sodium excretion decreased from 195 mmol (4.5 g)/day at baseline to 109 mmol (2.5 g)/day at 12 months in the treatment group, while the corresponding change in the control group was 181 mmol (4.2 g)/day to 166 mmol (3.8 g)/day. Compared with the control group, which experienced no change in left ventricular mass, the reduced-sodium group experi-

enced a mean reduction in left ventricular mass of 5.4 percent (from 238 to 225 g, $p < 0.05$ compared with the control).

In summary, available data from cross-sectional studies in hypertensive individuals are consistent in documenting a progressive, direct, and independent relationship between sodium intake and left ventricular mass. Furthermore, sodium may have a direct effect apart from an indirect effect mediated through blood pressure. While one controlled trial suggests that the association between sodium intake and left ventricular mass is causal, additional trials are needed.

Calcium Excretion, Bone Mineral Density, and Kidney Stones

Numerous intervention studies have demonstrated that increased sodium chloride intake induces a substantial increase in the urinary excretion of calcium (Table 6-19). Sodium chloride-induced hypercalciuria also appears to be accompanied by an increased intestinal calcium absorption (Breslau et al., 1982). However, the effects of sodium intake on biochemical markers of bone resorption (urinary pyridinoline and deoxypyridinoline) and bone formation (serum osteocalcin and bone-specific alkaline phosphatase) are uncertain. These markers were not affected by increasing sodium chloride intake in young women (Evans et al., 1997; Ginty et al., 1998), whereas sodium chloride-induced bone resorption was observed in postmenopausal women (Evans et al., 1997). A reduced sodium intake lowered serum osteocalcin in participants consuming the DASH diet but not those consuming a typical American diet (Lin et al., 2003). Compared with sodium chloride, sodium citrate "loading" induces the opposite effect on urinary calcium (Kurtz et al., 1987). Similarly, differing pressor and calciuric effects of sodium chloride and sodium bicarbonate or citrate have been widely reported (Kotchen, 1999; Luft et al., 1990; Sharma et al., 1992). However, when dietary sodium chloride is not reduced, dietary sodium bicarbonate loading has little effect on the urinary excretion of calcium (Lemann et al., 1989). In postmenopausal women in whom calcium excretion was increased by a high protein diet, replacing dietary sodium chloride with an equimolar amount of sodium bicarbonate promptly induced a sharp and sustained decrease in the urinary excretion of calcium (Lutz, 1984). In animals, bicarbonate acts directly on the renal tubule to increase its reclamation of calcium (Bomsztyk and Calalb, 1988).

While the effect of sodium intake on urinary calcium excretion is evident, calcium absorption was not tracked in these studies. Thus

TABLE 6-19 Intervention Studies on the Effect of Sodium Intake on Calcium Excretion

Reference	Study Design	Sodium (Na) Intake g/d (mmol/d)
McCarron et al., 1981	6 men 3–7 d	0.23 (10) 6.9 (300) 18.4 (800) 34.5 (1,500)
Breslau et al., 1982	13 men and women 10 d	0.23 (10) 5.8 (250)
Castenmiller et al., 1985	12 men 2 levels of Ca 3.2 mmol/MJ and 4.1 mmol/MJ 2 wk	 0.51 (22) 4.1 (178)
McParland et al., 1989	10 elderly women Low salt diet ± salt supplement 10 d	1.6 (70) 3.9 (170)
Zarkadas et al., 1989	17 postmenopausal women 89 mmol/d diet plus Na supplement of 1.2 g (51 mmol/d) or 2.3 (103 mmol/d) 4 d	2.0 (89) 3.2 (140) 4.4 (191)
Chan et al., 1992	7 men 5 d	1.2 (50) 5.8 (250)
Nordin et al., 1993	30 postmenopausal women	2.1 (90) 2.8 (120) 3.4 (150)
Sakhaee et al., 1993	14 men and women 10 d	1.2 (50) 6.9 (300)
Evans et al., 1997	11 premenopausal and 11 postmenopausal women 7 d	 1.2 (50) 6.9 (300)
Lietz et al., 1997	14 postmenopausal women 816 mg Ca 8 d	1.4 (60) 3.9 (170)
Ginty et al., 1998	16 women 14 d	 1.8 (80) 4.1 (180)
Lin et al., 2003	186 men and women 30-d crossover	 1.2 (50) 2.3 (100) 3.4 (150)

[a,b] Values with different superscripts differ significantly at $p < 0.05$.

Calcium (Ca) Excretion (mg/d)	
59	
124	
178	
262	
110 ± 14[a]	
167 ± 16[b]	
Low calcium diet (mmol Ca/mmol creatinine)	*High calcium diet (mmol Ca/mmol creatinine)*
0.25[a]	0.28[a]
0.31[b]	0.33[b]
83[a]	
106[b]	
128[a]	
148[b]	
152[b]	
Significant increase in Ca excretion with the addition of +1.2 g/d Na No difference between 1.2 g and 2.3 g/d Na	
126[a]	
192[b]	
136	
144	
176	
109[a]	
157[b]	
Premenopausal	*Postmenopausal*
0.38[a]	0.42[a]
0.52[b]	0.62[b]
160[a]	
180[b]	
Salt-sensitive (mmol Ca/mmol creatinine)	*Nonsensitive (mmol Ca/mmol creatinine)*
0.15[a]	0.15[a]
0.26[b]	0.14[a]
Control diet (mg Ca/g creatinine)	*DASH diet (mg Ca/g creatinine)*
88[a]	92[a]
97[a]	96[a]
110[b]	104[b]

the overall impact on calcium balance is unclear, as is the role of sodium intake on bone mineral density (Table 6-20). Although some epidemiological studies have reported an inverse effect of sodium intake on bone mineral density (Devine et al., 1995; Martini et al., 2000), this relationship was not apparent in other studies (Jones et al., 1997; Matkovic et al., 1995). The effects of a reduced sodium intake in preventing bone fractures has not been tested.

Hypercalciuria is a common risk factor for the formation of renal stones (Strauss et al., 1982). Individuals who were found to form calcium stones were reported to have a higher sodium chloride intake (14 g [239 mmol]/day) compared with healthy subjects (8 g [136 mmol]/day) (Martini et al., 1998). A prospective cohort study showed a significant trend ($p < 0.001$) for the risk of renal stones with increased sodium intake (Curhan et al., 1997). The risk of renal stones has been reported to increase with an increased sodium:potassium ratio (Stamler and Cirillo, 1997).

Pulmonary Function

Several studies have examined the relationship between sodium intake and bronchial responsiveness to agents (e.g., histamines) that cause airway constriction. In two surveys, bronchial reactivity was strongly and directly related to urinary sodium excretion after adjusting for age and cigarette smoking (Burney et al., 1986; Tribe et al., 1994). In analysis of NHANES III data (Schwartz and Weiss, 1990), bronchitis was positively associated with the dietary sodium:potassium ratio. However, other cross-sectional studies have not found a relationship (Britton et al., 1994; Zoia et al., 1995).

A low salt diet (3.75 g/day, containing 1.5 g [65 mmol] of sodium) improved while a high salt diet (13.75 g/day, containing 5.5 g [239 mmol] of sodium) worsened postexercise pulmonary function in subjects with exercise-induced asthma (Gotshall et al., 2000). When asthmatic patients were given 4.6 g (200 mmol)/day of dietary sodium, all measures of severity of asthma were adversely affected (Carey et al., 1993). Furthermore, salt loading (6.1 g/day, containing 2.4 g [105 mmol] of sodium) was found to worsen the symptoms of asthma (Medici et al., 1993).

Gastric Cancer

It has been hypothesized that high doses of salt can result in destruction of the mucosal barrier of the stomach such that the mucus membrane is easily invaded by carcinogens (Correa et al., 1975).

Indirect support for this hypothesis comes from observational studies of *Helicobacter pylori* infection. Specifically, seropositivity for *H. pylori* was directly related to gastric cancer mortality (Eurogast Study Group, 1993), and the prevalence of *H. pylori* has been associated with the intake of salty foods (Tsugane et al., 1994).

Evidence in laboratory animals indicates that high intakes of salt may increase the incidence of gastric cancer when animals are exposed to various carcinogens (Cohen and Roe, 1997). It has been suggested that salt exerts an enhancing effect on both the initiation and promotion steps of gastric carcinogenesis (Takahashi and Hasegawa, 1986). The evidence in humans is less clear because the source of available data is limited to epidemiological studies.

A number of cross-sectional studies have been conducted to evaluate the association between salt intake and risk of gastric cancer. A significant positive association was observed between sodium or salt intake (or sodium excretion) and incidence of gastric cancer in most (Bernstein and Henderson, 1985; Kneller et al., 1992; La Vecchia et al., 1997; Lee et al., 1995; Montes et al., 1985; Palli et al., 2001; Tsubono et al., 1997; Tsugane et al., 1991), but not all (Honjo et al., 1994; Ikeda et al., 1988) of these studies. More recently, the Intersalt study correlated gastric cancer mortality with sodium intake from 24 countries (Joossens et al., 1996). Multiple regression analysis of these data yielded a significant positive correlation ($p < 0.001$) of urinary sodium excretion with evidence of a threshold. Specifically, there was no increased incidence of cancer mortality below 117 mmol (2.7 g)/day in men and 91 mmol (2.1 g)/day in women. The RR for gastric cancer as determined from case-control studies ranged from 1.4 to 6.7 with higher intakes of salt (Boeing et al., 1991; Coggon et al., 1989; Graham et al., 1990; Hoshiyama and Sasaba, 1992; Lee et al., 1995; Nazario et al., 1993; Tuyns, 1983; You et al., 1988).

In the one available prospective study, salt intake was significantly and directly associated in a dose-response fashion with gastric cancer in men, but not in women (Tsugane et al., 2004).

Dose-Response Assessment

Adults

Data Selection. The model for establishing Tolerable Upper Intake Levels (ULs) (see Chapter 3) depends upon being able to identify a hazard or adverse effect associated with consumption of a nutrient at levels above an individual's requirement for the nutri-

TABLE 6-20 Epidemiological Studies on the Effect of Sodium Intake on Calcium Excretion, Bone Mineral Density, and Kidney Stones

Reference	Study Design[a]	Effect[b]
Urinary calcium excretion		
Short et al., 1988	12 men and women on 4 levels of Na and constant Ca 3-d planned diet	+
Nordin et al., 1993	220 women	+
Itoh and Suyama, 1996	Randomized population survey 410 men, 476 women	+
Dawson-Hughes et al., 1996	Cross-sectional 249 men, 665 women	+
Bone density		
Greendale et al., 1994	Longitudinal 258 women, 169 men	NS
Matkovic et al., 1995	Cross-sectional 381 women	+
Devine et al., 1995	Longitudinal 124 women	+
Jones et al., 1997	Population-based study 34 men, 120 women	NS
Kidney stones		
Burtis et al., 1994	124 subjects 1,000 mg Ca and defined diet or 1,000 mg Ca and usual diet	+
Curhan et al., 1997	Prospective cohort 903,849 subjects	+

Findings[c]
Urinary Na and Ca excretion were positively correlated in young men and women
Significant linear relationship between urinary Na and urinary Ca observed for both normal (n = 88) and osteoporotic (n = 132) postmenopausal women
Significant positive correlation between urinary Na and Ca in men and women
Urinary Na and Ca excretion were associated at moderate and high intakes of Ca but not low intakes in elderly men and women
No association between Na intake and BMD in men and women
Urinary Na found to be the most important determinant of urinary Ca excretion for 8- to 13-yr-old girls Urinary Ca (mmol/d) = 0.01154 × urinary Na (mmol/d) + 0.823, whereas Ca intake had relatively little impact No association with bone mass
Urinary Na excretion was significantly and negatively correlated with change (decrease) in bone density at the hip bone (–0.003 × urinary Na + 6.33) and interocanter site (–0.003 × urinary Na + 7.86) in postmenopausal women
Urinary Na correlated with urinary deoxypyridinoline and urinary Ca in men and women Urinary Na correlated with bone mineral content and density, but the association disappeared when adjusted for other confounders, especially body weight
Urinary Ca excretion increased by 0.77 mg/23 mg of Na excreted in individuals with Ca oxalate kidney stones
Relative risk for renal stones increased with increased intake of Na Q1 = 1.6 g/d Na, RR = 1.0 Q2 = 2.3 g/d Na, RR = 1.08 Q3 = 2.8 g/d Na, RR = 1.15 Q4 = 3.6 g/d Na, RR = 1.10 Q5 = 4.9 g/d Na, RR = 1.30

continued

TABLE 6-20 Continued

Reference	Study Design[a]	Effect[b]
Stamler and Cirillo, 1997	1,658 men, 1,967 women	+
Martini et al., 2000	47 men, 38 women	+

[a] Na = sodium; K = potassium, Ca = calcium.
[b] + means Na had a significant impact on Ca excretion or BMD. NS means Na did not have a significant effect on Ca excretion or BMD.
[c] Q = quartile or quintile, RR = relative risk, BMD = bone mineral density.

ent. The preferred type of adverse effect is a clinical outcome, such as evidence of mortality or serious morbidity that has been observed to occur in a few sensitive individuals as a direct result of consuming a nutrient above his or her needs. In situations in which the adverse effect is a chronic disease, it is possible to use clinical outcomes, such as total mortality, cause-specific mortality, or serious morbidity. The ideal type of study is an appropriately designed, long-term trial with multiple levels of nutrient intake.

However, for most nutrients, and particularly for those where adverse effects are related to chronic disease, trials with such endpoints are unavailable, especially dose-response trials that test multiple levels of intake. For sodium, trials with relevant clinical outcomes (e.g., fatal and nonfatal stroke, coronary heart disease, end-stage renal disease, kidney stones, or bone fractures) have not been conducted. In the absence of trials with clinical outcomes, a synthesis of evidence from available trials, observational studies, dose-response trials that link sodium to a well-accepted surrogate endpoint, and observational studies that link the chosen surrogate endpoint with specific clinical outcomes, must be used.

Blood Pressure as the Endpoint. Among the endpoints considered in the previous section, blood pressure stands apart in terms of the research database supporting its use as a biomarker for several diseases of substantial public health importance. Results from the most rigorous dose-response trials (see Appendix I) have documented a progressive, direct effect of dietary sodium intake on blood pressure in nonhypertensive and hypertensive individuals. Furthermore,

Findings[c]
An increased Na:K ratio was significantly ($p < 0.05$) and independently associated with increased prevalence of renal stones
Multiple regression analysis showed that a high salt intake (> 16 g/d) was an independent predictor of risk for low BMD in stone-forming men and premenopausal women estimated by food-frequency questionnaire

persuasive evidence from large-scale observational studies has documented a direct relationship between blood pressure and the risk of cardiovascular diseases (specifically stroke and coronary heart disease) and end-stage renal disease. The relationship of blood pressure to these diseases has been characterized as "strong, continuous, graded, consistent, independent, predictive, and etiologically significant" (JNC, 1997).

Other Possible Endpoints. Other endpoints or adverse effects were considered, including clinical cardiovascular outcomes (i.e., stroke and coronary heart disease), subclinical cardiovascular outcomes (i.e., left ventricular mass), and noncardiovascular outcomes (e.g., urinary calcium excretion, osteoporosis, gastric cancer, and asthma). For left ventricular mass, cross-sectional studies consistently document an association between urinary sodium excretion and left ventricular mass, but only one small, controlled trial assessed the effects of sodium reduction on this endpoint. For urinary calcium excretion, numerous trials documented that a reduced sodium intake lowers urinary calcium excretion, but urinary calcium excretion by itself is not a well-accepted surrogate marker for bone mineral density or dietary induced osteoporosis. Evidence that links sodium intake with gastric cancer is reasonably strong, but still insufficient to establish a UL. Data on the relationship between sodium intake and asthma are sparse.

Identification of a Lowest-Observed-Adverse-Effect Level (LOAEL). In aggregate, the relationship between sodium intake and blood pres-

sure is direct. While it would be best to have a marker for which a normal range has been accepted as not enhancing risk, based on data available there is no apparent threshold below which there is no increased risk for cardiovascular diseases across the range of blood pressures (≥ 115/70 mm Hg) typically observed in the United States and Canada (Burt et al., 1995; Joffres et al., 2001; Wolf-Maier et al., 2003). Recent studies on the relationship of blood pressure changes to subsequent risk of cardiovascular disease have documented increased risk in nonhypertensive persons, including those termed "prehypertensive." New guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure for classification of blood pressure and for hypertension prevention and management have been issued (Chobanian et al., 2003) that include a new category designated "prehypertension." This category combines the "normal" and "borderline" categories used in previous guidelines (JNC, 1997). Individuals with a systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg are now termed prehypertensive.[4] Prehypertensive individuals are at increased risk for progression to hypertension and for blood pressure-related cardiovascular diseases (Lewington et al., 2002).

The relationship between sodium intake and blood pressure is direct and progressive. Supportive evidence comes from observational studies and clinical trials (see Tables 6-11, 6-12, 6-13, and 6-15; Figure 6-5; and Appendix Table I). However, the potential for confounding, even in otherwise well-designed observational studies, is a concern. Likewise, the assessment of dose-response relationships in meta-analyses is subject to confounding. In this setting, the best available dose-response evidence comes from individual trials that specifically examined this issue (i.e., randomized trials that test the effects of three or more levels of sodium intake on blood pressure). In these dose-response studies, the lowest level of sodium intake spanned from approximately 0.23 g to 1.5 g (10 mmol to 65 mmol)/day, while the highest level spanned from approximately 3.2 g to over 34 g (140 mmol to 1,500 mmol)/day. The range (highest level minus lowest level) was thus 1.7 g (75 mmol)/day (Sacks et al., 2001) to 34.3 g (1,490 mmol)/day (Luft et al., 1979b). In all these dose-response trials, the average blood pressure at the lowest level of intake would not be considered low, even at a sodium intake

[4] The "hypertension" category continues to be defined as blood pressure ≥ 140/90 mm Hg.

of 0.23 g (10 mmol), an amount that is below the Adequate Intake (AI) for younger adults.

Most relevant to determining a UL are the three trials in which the lowest level of dietary sodium intake was close to the AI (Johnson et al., 2001; MacGregor et al., 1989; Sacks et al., 2001). When dietary sodium was provided at the average level of 1.2 g (50 mmol)/day, blood pressure was significantly less than when the target average sodium intake was 2.3 g (100 mmol)/day (Sacks et al., 2001). This pattern of findings was evident in the control diet, which was typical of what many Americans eat, as well as in the DASH diet, which was close to recent dietary guidelines. Blood pressure reductions from a reduced sodium intake were also demonstrated in pertinent subgroups (see Table 6-14).

Two other dose-response trials included levels of sodium intake that were close to 1.2 and 2.3 g (50 and 100 mmol)/day (Johnson et al., 2001; MacGregor et al., 1989). Both of these trials documented reduced blood pressure across this span of sodium intake; however, both trials were considerably smaller in size than the trial by Sacks and colleagues, and the trial by MacGregor and colleagues enrolled only individuals with hypertension.

In view of the results from these three trials, the lowest-observed-adverse-effect level (LOAEL) for dietary sodium is set at 2.3 g/day (100 mmol/day). It is recognized that the term LOAEL as applied to dietary sodium is a point on a continuous relationship with blood pressure, a point that corresponds to the next level above the AI that was tested in dose-response trials. As with other nutrients, a no-observed-adverse-effect level (NOAEL) would have been preferable. However, in the setting of a progressive, dose-response relationship without a threshold, a NOAEL cannot be set. Note that the UL is not a recommended intake. As with other ULs, there is no apparent benefit to consuming levels above the AI.

Uncertainty Assessment. Identification of the NOAEL for sodium is complicated. Available data strongly support the desirability of reducing blood pressure as a means to reduce the risk of cardiovascular disease. Recent evidence indicates that blood pressures as low as 115/70 mm Hg should be cardioprotective. However, in addition to sodium intake, several dietary and nondietary factors also affect blood pressure. Furthermore, the rise in blood pressure in response to increased dietary sodium intake is heterogeneous and is blunted in the setting of dietary potassium intakes in the range of the AI (4.7 g [120 mmol]/day) (Morgan et al., 1982; Morris et al., 1999; Weinberger et al., 1982), a mineral-rich diet (Sacks et al., 2001),

and perhaps other dietary factors, such as high dietary calcium intake (Rich et al., 1991; Saito et al., 1989).

Nondietary factors, such as age, race, specific genes, and the presence of hypertension, diabetes, or kidney disease, also affect the blood pressure response to changes in dietary sodium intake. Specifically, older-age persons, African-Americans, hypertensive individuals, and persons with diabetes or chronic kidney disease tend to be more salt sensitive than their counterparts. There is also demonstrated heterogeneity in the extent of cardiovascular disease risk reduction from a given reduction in blood pressure.

In the UL model (see Chapter 3), when there is concern that adverse effects may occur at levels of intake lower than the LOAEL or NOAEL, an uncertainty factor (UF) is used to adjust downward the LOAEL or NOAEL in order to derive the UL. The UL is defined as the highest level of intake consumed on a chronic basis at which no increased risk of serious adverse effects will occur. As indicated in Chapter 3, the UF is set at 1.0 when there is convincing evidence that the identified adverse effects do not occur at the observed NOAEL, but do occur at higher levels. The UF is set at greater than 1.0 when there is less convincing evidence that a true NOAEL has been demonstrated—there remains the possibility that adverse effects may occur at intakes below the NOAEL, even though they have not been documented. The UF is also greater than 1.0 when data demonstrating a NOAEL are unavailable, but data indicating a LOAEL are available.

For sodium, the UF could be set at greater than 1.0, because there are large numbers of persons who would achieve an even lower blood pressure by reducing their sodium intake from the LOAEL to lower levels. However, the actual NOAEL for these individuals is unknown. Choosing a level of sodium intake at which no one would experience a rise in blood pressure would be difficult because there is heterogeneity in both the extent of blood pressure reduction that would be achieved and in the extent of cardiovascular disease risk reduction. Also, consuming a diet with sodium intake level at the NOAEL may well result in a diet inadequate in other essential nutrients, particularly for those with lower levels of energy expenditure. Lastly, a UF of approximately 1.6 or higher would lead to a UL below the AI. In view of these considerations, the UF for sodium is set at 1.0.

Derivation of a UL. The LOAEL of 2.3 g (100 mmol)/day was divided by the UF of 1.0 to derive a UL of 2.3 g (40 mmol)/day for total sodium intake.

$$\text{UL} = \frac{\text{LOAEL}}{\text{UF}} = \frac{2.3 \text{ g/day}}{1.0} = 2.3 \text{ g (100 mmol)/day}$$

Similar to the sodium AI, the sodium UL is based on moderate physical activity (nonstrenuous physical activity) and based on usual energy intakes as cited for each age group under "Findings by Life Stage and Gender Group."

Sodium and Chloride UL Summary, Ages 19 Through 50 Years

Much of the data used to set the UL were derived from trials that included both young and middle-aged adults. Hence this UL applies to men and women ages 19 to 50 years. Since chloride is assumed to be in foods in equimolar amounts, the UL for chloride is set at an equimolar basis, 3.6 g (100 mmol)/day.

UL for Sodium for Adults

19–50 years	**2.3 g (100 mmol)/day of sodium**

UL for Chloride for Adults

19–50 years	**3.6 g (100 mmol)/day of chloride**

Older Adults and the Elderly Ages 51+ Years

In observational studies, the rise in blood pressure in response to higher sodium intake increases with age (Law et al., 1991a). In trials, middle- and older-age persons (> 45 years) have greater sensitivity to changes in sodium intake than younger adults (Vollmer et al., 2001). As documented previously, elderly persons are especially sensitive to changes in sodium intake (Johnson et al., 2001). Common problems in aging are excessive retention of sodium and volume overload. In elderly, the capacity to excrete sodium, as well as the diurnal variation in its excretion, are altered. Both the decrease in glomerular filtration rate and reduced responsiveness of the renin-angiotensin-aldosterone system seen with aging are major factors that limit the ability of the kidney to excrete an acute sodium load. Other factors, such as dopamine, prostaglandins, intrarenal hemodynamics, activity of the α-adrenergic system within the kidney, and renal nerve activity, may also play a role.

Sodium and Chloride UL Summary, Ages 51+ Years

Because of increased salt sensitivity in the elderly and due to the higher risk of blood pressure-related cardiovascular disease, the UL

for sodium should be less than 2.3 g (100 mmol)/day. However, data are insufficient to precisely define this level, and many in this age group are under medical supervision due to hypertension, and thus the UL would not apply. In this setting, the UL for sodium and for chloride remain the same as for younger individuals.

UL for Sodium for Older Adults

51+ years	**2.3 g (100 mmol)/day of sodium**

UL for Chloride for Older Adults

51+ years	**3.6 g (100 mmol)/day of chloride**

Pregnancy and Lactation

According to some authorities, pregnant women retain sodium. Hence salt restriction and prophylactic diuretics have been prescribed to avoid the appearance of de novo hypertension during gestation (Brown and Gallery, 1994; Chesley, 1978; Collins et al., 1985; Lindheimer and Katz, 1985, 2000; Steegers et al., 1991a). Alternatively, data suggest that the pregnant woman may be prone to subtle salt wasting and thus providing additional sodium has been suggested in order to avoid preeclampsia (Robinson, 1958). Still another view is that pregnant women handle ingested sodium similar to the way they do in the nonpregnant state, albeit around new set points for extracellular volume and for volume-influencing hormones (Brown and Gallery, 1994; Lindheimer and Katz, 2000; Weinberger et al., 1977).

Hypertensive disorders during pregnancy are an important cause of maternal and perinatal morbidity and mortality. Among these disorders are chronic hypertension that antedates the pregnancy, gestational hypertension, and preeclampsia. Preeclampsia is a serious condition characterized by the occurrence of hypertension, edema, and proteinuria after 20 weeks of gestation in previously nonhypertensive women. While the pathogenesis of preeclampsia remains uncertain, in the past attention has focused on nutritional factors, particularly a high sodium intake and low calcium intake as possible etiological factors. In fact, low sodium diets have been routinely prescribed as a means to prevent preeclampsia and its complications (Churchill and Beevers, 1999).

However, recent clinical research that included both observational studies (Franx et al., 1999; Morris et al., 2001) and clinical trials (Knuist et al., 1998; Steegers et al., 1991b; van der Maten et

al., 1997) has documented that sodium reduction had no apparent benefit in lowering blood pressure or preventing pregnancy-induced hypertension or its complications. Neither was there any evidence of adverse effects on obstetrical outcomes from sodium reduction in these studies. In the three clinical trials, the mean urinary sodium excretion values in the control and reduced sodium groups were approximately 130 mmol (2.9 g)/day versus 60 mmol (1.4 g)/day (Steegers et al., 1991b), 124 mmol (2.8 g)/day versus 84 mmol (1.9 g)/day (Knuist et al., 1998), and 142 mmol (3.3 g)/day versus 61 mmol (1.4 g)/day (van der Maten et al., 1997). Hence, available evidence indicates that reducing sodium intake has little impact on preventing hypertensive disorders of pregnancy or their complications.

Overall, there is inadequate evidence to support a different upper intake level for sodium intake in pregnant women from that of nonpregnant women as a means to prevent hypertensive disorders of pregnancy. Also, there are inadequate data to justify a different UL for lactating women. Therefore, the ULs for sodium for pregnant and for lactating women are the same as for nonpregnant women. Similarly, there is no data to indicate that chloride is handled differently during pregnancy or lactation; thus the ULs for chloride remain the same as for the nonpregnant and nonlactating states.

Sodium and Chloride UL Summary, Pregnancy and Lactation

UL for Sodium, Pregnancy	
14–18 years	**2.3 g (100 mmol)/day of sodium**
19–50 years	**2.3 g (100 mmol)/day of sodium**
UL for Sodium, Lactation	
14–18 years	**2.3 g (100 mmol)/day of sodium**
19–50 years	**2.3 g (100 mmol)/day of sodium**
UL for Chloride, Pregnancy	
14–18 years	**3.6 g (100 mmol)/day of chloride**
19–50 years	**3.6 g (100 mmol)/day of chloride**
UL for Chloride, Lactation	
14–18 years	**3.6 g (100 mmol)/day of chloride**
19–50 years	**3.6 g (100 mmol)/day of chloride**

Infants

Little information is available on the effects of sodium on blood pressure in infants. The effect of two levels of dietary sodium on blood pressure and dynamic skinfold thickness was examined in 124 infants (Bernstein et al., 1990). Newborn infants were fed one of three diets: 43 infants were exclusively fed human milk (0.15 g of sodium [6.6 mmol]/L), 42 infants were fed a low sodium formula containing 0.23 g of sodium [10.2 mmol/L]), and 39 infants were fed a formula containing 0.31 g of sodium (13.9 mmol)/L. There were no significant differences among the three groups for either dynamic skinfold thickness or blood pressure at 6 weeks of age.

The data on the role of sodium intake during infancy on blood pressure in later years are also very limited. The most rigorous study was conducted with infants in Holland with a subsequent follow-up 15 years later. In this randomized, controlled trial of 476 Dutch infants fed a usual (≈ 0.33 g [≈ 14.3 mmol]/day) or low sodium (≈ 0.12 g [≈ 5.1 mmol]/day) formula, there was a small but significant reduction in blood pressure at 6 months among infants fed the low sodium formula (Hofman et al., 1983). After 25 weeks of age, systolic blood pressure in the low sodium group was 2.1 mm Hg lower ($p < 0.01$) than the normal sodium group. A 15-year follow-up of these children revealed that adjusted systolic and diastolic blood pressures were 3.6 mm Hg and 2.2 mm Hg lower, respectively, in children who had been assigned the low sodium diet during infancy (Geleijnse et al., 1997).

Although not frequently seen, hypernatremic dehydration has been reported in exclusively breast-fed infants (Kini et al., 1995; LSRO, 1998; Peters, 1989; Sofer et al., 1993). Sodium concentrations of the human milk consumed by some of these infants with hypernatremic dehydration ranged from 0.71 to 2.1 g (31 to 92 mmol)/L, which is significantly above the estimated typical content of human milk (0.13 to 0.16 g [5.6 to 7.0 mmol]/L) (see Table 6-8) (Kini et al., 1995; LSRO, 1998).

For infants, a UL could not be established because of insufficient data documenting the adverse effects of chronic intakes of overconsumption of sodium in this age group. To prevent high levels of sodium chloride intake, the only source of intake for infants should be human milk (or formula) and food to which as little sodium as possible is added during processing. Although evidence is limited, the potential long-term effects of reduced sodium formulas on blood pressure measured 15 years later (Geleijnse et al., 1997) suggest persistent adverse effects. Hence, as with other nu-

trients, an intake of sodium or chloride markedly above the AI is not warranted.

Sodium and Chloride UL Summary, Infants

UL for Sodium for Infants

0–12 months	**Not possible to establish; source of intake should be from human milk (or formula) and food only.**

UL for Chloride for Infants

0–12 months	**Not possible to establish; source of intake should be from human milk (or formula) and food only.**

Children and Adolescents

Concerns about adverse effects related to sodium intake in children are focused in two areas: first, does a higher level of dietary sodium result in increased blood pressure in children—to the extent that there is a definable increase in risk of cardiovascular disease in children, and second, does increased dietary intake of sodium during childhood track to increased blood pressure during adulthood and thus increased risk for subsequent cardiovascular disease.

The extent to which blood pressure in childhood affects subsequent blood pressure and chronic disease risk in adulthood has been evaluated in a number of studies. Studies that have examined the effects of sodium intake on blood pressure in children include observational studies (Cooper et al., 1983; Geleijnse et al., 1990; Robertson, 1984; Simon et al., 1994; Tucker et al., 1989) and, to a lesser extent, randomized, controlled-design clinical trials (Calabrese and Tuthill, 1985; Cooper et al., 1984; Ellison et al., 1989; Gillum et al., 1981; Howe et al., 1985, 1991; Sinaiko et al., 1993), as well as a study of twins and siblings (Miller and Weinberger, 1986; Miller et al., 1988). A recent review of these studies has been published (Simons-Morton and Obarzanek, 1997).

Many of these studies had methodological limitations, including small sample size, suboptimal blood pressure measurements, and limited experimental contrast. A longitudinal cohort of 233 children (5 to 17 years of age) did not reveal an association between sodium excretion and change in blood pressure over time (Geleijnse et al., 1990). When sodium intake was reduced to less than 1.4 g (60 mmol)/day in 149 nonhypertensive children ages 2.6 to 19.8 years, a small decrease in the average systolic, diastolic, or

mean arterial blood pressure was seen (Miller and Weinberger, 1986; Miller et al., 1988). In another trial of 80 hypertensive children (6 to 9 years old) with sodium intakes of 2.0 g (87 mmol)/day versus 2.9 g (130 mmol)/day, there were no significant reductions in blood pressure (Gillum et al., 1981), possibly because of the limited contrast in sodium intake.

In a controlled trial of adolescents, a 3-year reduced sodium intervention lowered the age-related increase in systolic and diastolic blood pressure in girls, but not in boys (Sinaiko et al., 1993). As in other trials, the contrast in urinary sodium excretion was small.

Overall, available evidence on the effects of sodium reduction on blood pressure in children is limited and inconsistent. Hence there are insufficient data to directly set a UL based on expected blood pressure change. Therefore, the ULs for children and adolescents were determined by extrapolating from the adult ULs based on averages of median energy intakes as was used for setting the AIs for children.

Extrapolation of the adult UL to children is appropriate. Numerous observational studies have documented that blood pressure tracks with age from childhood into the adult years (Bao et al., 1995; Dekkers et al., 2002; Gillman et al., 1993; Van Lenthe et al., 1994). Further, it is increasingly recognized that the antecedents of chronic conditions in adults, such as elevated blood pressure and atherosclerosis, occur in childhood.

The median energy intake for adults was 2,150 kcal/day. For children 1–3, 4–8, and 9–13 years of age, the median energy intakes were 1,372, 1,757, and 2,042 kcal/day, respectively. The ULs for children are extrapolated from the adult UL of 2.3g (100 mmol)/day based on these estimated energy intakes, after rounding. Since the estimated energy intake for adolescents is in the same range as adults, the ULs for this age group are the same as those for adults.

Sodium and Chloride UL Summary, Ages 1 Through 18 Years

UL for Sodium for Children	
1–3 years	**1.5 g (65 mmol)/day of sodium**
4–8 years	**1.9 g (83 mmol)/day of sodium**
9–13 years	**2.2 g (95 mmol)/day of sodium**
UL for Sodium for Adolescents	
14–18 years	**2.3 g (100 mmol)/day of sodium**

UL for Chloride for Children

1–3 years	**2.3 g (65 mmol)/day of chloride**
4–8 years	**2.9 g (83 mmol)/day of chloride**
9–13 years	**3.4 g (95 mmol)/day of chloride**

UL for Chloride for Adolescents

14–18 years	**3.6 g (100 mmol)/day of chloride**

Factors Affecting the Tolerable Upper Intake Level

Salt Sensitivity

As discussed previously, blood pressure, on average, is directly related to dietary sodium intake. However, evidence from a variety of studies, including observational studies and clinical trials, has demonstrated heterogeneity in the blood pressure responses to sodium intake. Those individuals with the greatest reductions in blood pressure in response to decreased sodium intake are termed "salt sensitive" (Kawasaki et al, 1978; Miller et al., 1983; Morris et al., 1999; Sullivan et al., 1980; Weinberger, 1996) (see Box 6-1). Some studies have documented that salt sensitivity is reproducible over time (Weinberger and Fineberg et al., 1991) and that salt sensitivity as assessed by two different techniques is highly correlated (Weinberger et al., 1993a).

A variety of factors influence the blood pressure response to changes in sodium intake. Some factors, particular dietary factors, are modifiable, while other factors are fixed, such as genetic factors. Several factors are acquired, such as advanced age and chronic medical conditions, specifically, hypertension, diabetes, and chronic kidney disease.

Salt-sensitive hypertensive individuals are at an increased risk for cardiovascular events (Morimoto et al., 1997). Salt sensitivity, even in those who are nonhypertensive, also increases the risk of incident hypertension and cardiovascular death (Weinberger et al., 2001). At present, an agreed upon definition and practical tools to measure salt sensitivity in individuals are unavailable. Hence even though individuals who are considered salt sensitive should benefit from a level of sodium intake below the UL of 2.3 g (100 mmol)/day, there is no practical strategy to identify such individuals, except perhaps by identifying specific subgroups of the population with a high prevalence of salt sensitivity (i.e., older-aged individuals, African Americans, and individuals with hypertension, diabetes, or chronic kidney disease).

BOX 6-1 Definition of Salt Sensitivity

The prevalence of salt sensitivity depends on the definition. Relevant aspects of the definition include the type of blood pressure measured (systolic, diastolic, or mean arterial pressure), the types of thresholds reported (absolute mm Hg or percent change), the classification scheme (common categories are "salt sensitive" and "salt resistant"), the thresholds applied to the classification categories, the contrast in sodium intake tested (lowest and highest levels), and the mode of sodium delivery (diet versus rapid intravenous infusion). In one study, 73 percent of African Americans with hypertension and 56 percent of hypertensive white subjects were found to be salt sensitive, whereas in normotensive African-American and white subjects, only 36 and 29 percent, respectively, were salt sensitive (Weinberger et al., 1986).

Despite the use of the terms salt sensitive and salt resistant to classify individuals in research studies, the change in blood pressure in response to a change in salt intake is not binary. Rather, the reduction in blood pressure from a reduced sodium intake has a continuous distribution with individuals having greater or lesser degrees of blood pressure reduction. Hence, persons termed salt resistant may actually achieve some blood pressure reduction, just less than that achieved in salt-senstive persons.

In these groups, which together comprise a large fraction of the population of the United States and Canada, the UL should be lower than 2.3 g (100 mmol)/day. However, it is not possible at this time to precisely define such a level.

Interaction with Other Dietary Factors

In addition to sodium intake, the intake of potassium and perhaps other electrolytes (calcium and magnesium) also affects blood pressure. Further, the intake of these electrolytes, particularly potassium, may influence the blood pressure response to changes in dietary sodium intake. Sodium intake may also influence urinary excretion of these electrolytes.

Potassium. In observational studies, the ratio of sodium to potassium intake is often more strongly associated with blood pressure than either sodium intake alone (Rose et al., 1988) or potassium intake alone, especially in older-aged individuals (Khaw and Barrett-Connor, 1988). In clinical trials, increased potassium intake lowers blood pressure, and the effects of potassium in reducing blood pressure appear to be greatest when sodium is concurrently high (see

Chapter 5). Increased potassium intake also reduces the sensitivity of blood pressure to changes in sodium intake (Morris et al., 1999). The level of sodium intake does not appear to influence potassium excretion (Bruun et al., 1990; Castenmiller et al., 1985; Overlack et al., 1993; Sharma et al., 1990; Sullivan et al., 1980), except at levels of sodium intake above 6.9 g (300 mmol)/day, at which net loss of potassium has been demonstrated (Kirkendall et al., 1976).

Calcium. In observational studies, an inverse association between calcium intake and blood pressure has been reported (Cutler and Brittain, 1990; Witteman et al., 1989). Pooled analysis of clinical trials showed reductions in systolic and diastolic blood pressure of 0.89 to 1.44 mm Hg and 0.18 to 0.84 mm Hg, respectively, with calcium supplementation (400 to 2,000 mg/day) (Allender et al., 1996; Bucher et al., 1996; Griffith et al., 1999).

The level of sodium intake may affect the blood pressure response to increased calcium intake, and conversely, the level of calcium intake may affect the blood pressure response to sodium. In a small cross-sectional study, sodium intake was associated with increased blood pressure only at a low calcium intake (Hamet et al., 1991). In three small trials, calcium supplementation attenuated the effect of a high sodium intake on blood pressure (Rich et al., 1991; Saito et al., 1989; Zemel et al., 1986). In a crossover trial that tested the effects on blood pressure of calcium supplementation, only individuals previously classified as salt sensitive had a significant reduction in blood pressure, whereas persons classified as nonsalt-sensitive experienced no such reduction (Weinberger et al., 1993b). As described previously, higher levels of sodium intake increase the urinary excretion of calcium. Such observations highlight the complex interactions of dietary sodium and calcium on blood pressure.

Magnesium. Magnesium has been reported to lower blood pressure. While studies have been inconsistent, an analysis of 29 observational studies concluded that there was an inverse association between dietary magnesium and blood pressure (Mizushima et al., 1998). However, in a pooled analysis of 20 randomized clinical trials, there was no clear effect of magnesium intake on blood pressure (Jee et al., 2002). Data on the effects of sodium intake on magnesium excretion are limited. One study concluded that salt reduction (at levels of 1 to 2 g [43 to 87 mmol]/day) for 3 days did not influence magnesium excretion (Murayama and Taguchi, 1988).

Interactions Among Electrolytes. Interactions among all dietary electrolytes may be relevant. In the DASH diet, which was rich in potassium, calcium, and magnesium, sodium reduction lowered blood pressure, but to a lesser extent than that observed when subjects consumed a typical American diet that was comparatively low in these nutrients (Sacks et al., 2001). While this interaction and the previously described interactions of dietary potassium and calcium raise the possibility that the UL for sodium should be modified, available evidence is insufficient to adjust the UL based on concurrent intakes of these other nutrients.

Weight

A substantial body of evidence has documented that weight is directly related to blood pressure and that weight loss reduces blood pressure (Neter et al., 2003). There is also a strong biological basis for believing that increased weight should modify the blood pressure response to sodium intake. Obesity increases sympathetic nervous system activity, activates the renin-angiotensin-aldosterone system, and increases renal medullary compression, each of which increases tubular reabsorption of sodium and impairs sodium excretion (Hall et al., 2003). However, empirical evidence is inconsistent. In some studies, overweight was associated with an increased blood pressure response to a high sodium intake (Rocchini et al., 1989). In contrast, in a large trial that explicitly tested for an interaction, sodium reduction lowered blood pressure similarly in both nonobese and obese participants (see Table 6-14).

Overall, it is unclear whether obese individuals are more salt sensitive than nonobese individuals. Available evidence is insufficient to adjust the UL based on obesity status.

Gender

Observational studies and clinical trials provide some evidence that the blood pressure response to a reduced sodium intake may differ by gender. In the Intersalt study, an observational study that enrolled men and women aged 20 to 59 years, the direct association of blood pressure with 24-hour urinary sodium excretion was greater in women than in men (Stamler et al., 1991). In another large international study, blood pressure was directly and significantly associated with sodium intake in men, but nonsignificantly in women (Yamori et al., 1990). In subsequent analyses of this study, stratified by menopausal status, the direct relationship of blood pres-

sure to sodium intake was significant in postmenopausal women, but nonsignificant in premenopausal women (Yamori et al., 2001).

Evidence from clinical trials is likewise inconsistent. In subgroup analyses of Phase 1 of the Trials of Hypertension Prevention, which enrolled adults aged 30 to 54 years, a reduced sodium intervention led to significantly greater systolic blood pressure reduction in women compared with men; this finding may have resulted from a lower achieved level of sodium intake in women (Kumanyika et al., 1993). In the DASH-Sodium trial (see Table 6-14), sodium reduction lowered blood pressure in both men and women in both a typical American diet and the DASH diet. In the DASH diet, the systolic blood pressure reduction in women was significantly greater than that of the men. In a meta-analysis that explored the effects of gender on the blood pressure response to a reduced sodium intake, there was no significant difference in the blood pressure response in trials that enrolled at least 50 percent women versus those that enrolled less than 50 percent women (Geleijnse et al., 2003).

Overall, it is unclear whether women are more salt sensitive than men. Thus, the UL is set at the same level for men and women.

Hypertension

As previously described, a substantial body of evidence has documented that sodium reduction lowers blood pressure to a greater extent in hypertensive than in nonhypertensive individuals. These studies were typically conducted in hypertensive individuals not on medication. In individuals on antihypertensive drug therapy, sodium reduction can further lower blood pressure (Appel et al., 2001). In the setting of hypertension, the UL should be lower than 2.3 g (100 mmol)/day. However, it is not possible at this time to precisely define such a level.

Diabetes

Individuals with diabetes have increased total body sodium, increased renal tubular sodium reabsorption, and an impaired ability to excrete a sodium load compared with individuals without diabetes (de Chatel et al., 1977; Roland et al., 1986). Inadequate suppression of the renin-angiotensin-aldosterone system may be partly responsible for these effects (de Chatel et al., 1977). Increased salt sensitivity, as well as increased weight, may contribute to the high prevalence of hypertension in diabetics (Tuck et al., 1990). Few randomized trials have tested the effects of sodium reduction on

blood pressure in diabetics. In a trial of 16 type 1 diabetic patients with nephropathy who increased their normal intake by 2.3 g (100 mmol)/day, a significant rise in diastolic blood pressure and a nonsignificant rise in systolic blood pressure were observed (Mulhauser et al., 1996). In a trial of 34 individuals with type 2 diabetes with hypertension, a reduction of sodium intake from approximately 4.6 to 3.1 g (199 to 137 mmol)/day significantly lowered systolic blood pressure by 11.9 mm Hg, but did not lower diastolic blood pressure (Dodson et al., 1989). In a trial of 20 individuals with type 2 diabetes, which tested the effects of sodium reduction in the setting of drug therapy (i.e., an angiotensin-II receptor blocker), sodium reduction further lowered both systolic and diastolic blood pressure (Houlihan et al., 2002). Overall, available data indicate that persons with diabetes should be salt sensitive. In this setting, the UL should be lower than 2.3 g (100 mmol)/day. However, it is not possible at this time to precisely define such a level.

Chronic Kidney Disease

Animal studies and a variety of clinical research studies have documented that altered renal sodium handling occurs in the setting of chronic kidney disease (Strazzullo et al., 2003). It has also been postulated that subtle, acquired defects in renal sodium handling cause hypertension prior to the onset of chronic kidney disease (Johnson et al., 2002). In chronic kidney disease, sodium retention can raise blood pressure and may have detrimental effects on kidney function by inducing hyperfiltration and increasing filtration fraction and glomerular pressure. In a cross-sectional study of 839 nonhypertensive and hypertensive individuals, there was a direct, positive relationship between sodium intake and urinary albumin excretion (du Cailar et al., 2002). However, no randomized trial has specifically examined the effects of different levels of sodium intake on blood pressure and kidney function in the setting of chronic kidney disease.

Despite the absence of empirical evidence from controlled trials, available data suggest that as chronic kidney disease progresses, salt sensitivity increases. Dietary sodium reduction is routinely recommended as a way to reduce volume expansion and lower blood pressure in patients with chronic kidney disease, particularly at advanced stages. In the setting of chronic kidney disease, the UL should be lower than 2.3 g (100 mmol)/day. However, it is not possible at this time to precisely define such a level.

Genetic Factors

A rapidly increasing body of evidence indicates that genetic factors affect blood pressure levels and the blood pressure response to a reduced sodium intake. Several genotypes that influence blood pressure have been identified. Most of these genotypes influence the renin-angiotensin-aldosterone axis or renal salt handling. Consequently, these genotypes likely affect salt sensitivity. In a line of investigation that focused on Mendelian diseases associated with either high or low blood pressure, six genes associated with higher blood pressure and another eight genes associated with lower blood pressure have been identified (Lifton et al., 2002). It is noteworthy that each of these genes regulates renal sodium chloride handling—mutations that increase net sodium chloride reabsorption raised blood pressure, while mutations that reduce sodium chloride reabsorption lowered blood pressure.

Glucocorticoid-remediable aldosteronism is an example of a disease associated with increased sodium reabsorption. In this autosomal-dominant condition associated with severe hypertension, chronic aldosterone secretion leads to increased intravascular volume. An example of a Mendelian disease associated with salt wasting is Gitelman's syndrome. In analyses that compared blood pressure and urinary sodium excretion in individuals from a large group of related persons who carried zero, one, or two copies of the mutant gene, lower blood pressure was seen in those with two copies of the mutant gene (homozygotes) compared with those with no copy (wildtype) or one copy (heterozygotes). Both the homozygotes and heterozygotes consumed more salt than their wild-type relatives, indicating dietary compensation for their renal salt losses. Hence, although renal salt wasting leads to lower blood pressure in Gitelman's syndrome, there was actually an inverse relationship between salt intake and blood pressure. These Mendelian conditions, while uncommon, demonstrate the importance of renal sodium chloride handling as a determinant of blood pressure.

Three trials have tested whether certain genotypes modify the blood pressure response to a reduced salt intake. In subgroup analyses (n = 1,509) from Phase II of the Trials of Hypertension Prevention (Hunt et al., 1998), a reduced sodium intervention significantly lowered the risk of developing hypertension over 3 years in those with the AA genotype of the angiotensinogen gene, but not those with the GG genotype. Those individuals with the AG genotype tended to have an intermediate phenotype. Because the GG genotype is uncommon in African Americans, this study focused only on

white subjects, of whom 20 percent had the AA genotype, 48 percent the AG genotype, and 32 percent the GG genotype.

In a separate trial of 86 hypertensive men and women, genotypic variation in the M235T locus of the angiotensinogen gene was evaluated to determine if it affects the blood pressure response to a low-sodium mineral salt (Hunt et al., 1999). Over the 6 months of follow-up, those with the TT and MT genotypes had greater blood pressure reductions than those with the MM genotype. In a third trial that enrolled 46 persons aged 60 years and older, there was a direct dose-response between reported salt intake and both systolic and diastolic blood pressure (Johnson et al., 2001). Angiotensinogen genotypes appeared to influence the effects of sodium intake on diastolic blood pressure, but not systolic blood pressure.

Genetic variation of the angiotensinogen gene appears to modulate the blood pressure response to other nonpharmacologic interventions. Specifically, the AA genotype compared with the GG genotype has been associated with a greater blood pressure reduction from weight loss (Hunt et al., 1998) and from the DASH diet (Svetkey et al., 2001).

While it is interesting to speculate that genotyping might assist in developing nutritional guidelines to target those most likely, or those least likely, to benefit from a reduced sodium intake, currently available data are insufficient to modify the UL.

Risk Characterization

Data from the Third National Health and Nutrition Examination Survey (NHANES III) (Appendix Table D-8) indicate that more than 95 percent of men and 75 percent of women in the United States consumed in excess of the Tolerable Upper Intake Level (UL). Because estimates of sodium intake in NHANES III do not include sodium directly added to foods while eating (e.g., from the salt shaker), it is likely that a higher percentage of adults have intakes that exceed the UL. In phase I of the same survey (Burt et al., 1995), 24.7 percent of men and 24.3 percent of women 18 years of age and older had hypertension, meaning that a substantial number of individuals appear to experience this adverse effect identified in the risk assessment related to sodium.

Data on Canadian consumption (Appendix Table F-3) indicate that 90 to 95 percent of younger men (aged 19 to 50 years) and between 50 and 75 percent of younger women had usual intakes above the UL. Again, this does not include discretionary salt usage.

RESEARCH RECOMMENDATIONS

The effects of sodium on health have been debated, often vociferously (Alderman, 2002; deWardener, 1999; Perry, 2003). Over the past decade, key evidence has emerged that has informed this debate and which has, in general, strengthened the case for sodium reduction in the general population. Specific developments include: (1) dose-response trials that have documented a direct, progressive relationship between sodium intake and blood pressure in a broad range of individuals, including nonhypertensive persons, and (2) appropriately designed, prospective observational studies that have linked sodium intake with subsequent cardiovascular disease. Still, others argue that sodium reduction has adverse metabolic effects (e.g., increased plasma renin activity and perhaps insulin resistance), that sodium reduction has little or no effect on blood pressure in many individuals, and that other dimensions of diet (e.g., increased potassium intake or adoption of a mineral-rich diet) mitigate the harmful effects of dietary sodium on blood pressure in some individuals. Conversely, proponents of sodium reduction argue that sodium reduction could have benefits beyond blood pressure, including a reduced risk of left ventricular hypertrophy, osteoporosis, and gastric cancer.

Given the issues outlined above, some have argued for a large-scale, long-term trial that tests the effects of sodium reduction on clinical outcomes, including total mortality—while many have argued that such an undertaking is not feasible. Indeed, one major aspect of the sodium debate pertains to the level of evidence that is sufficient to guide policy in the absence of definitive trials that might be impossible to conduct.

As for most other nutrients, the absence of such a trial does not preclude the identification of reference values for dietary sodium intake. Given available evidence, it is concluded that a reduced sodium intake lowers blood pressure and that lower levels of blood pressure should reduce the risk of cardiovascular disease. Evidence of other potential benefits of sodium reduction was either inconclusive or insufficient to set reference values. Importantly, there was no credible evidence of harm from sodium intakes at or above the Adequate Intake (AI).

It is well-recognized that the current intake of sodium for most individuals in the United States and Canada greatly exceeds both the AI and the Tolerable Upper Intake Level (UL). Progress in achieving a reduced sodium intake will be challenging and will likely be incremental. Changes in individual behavior toward salt con-

sumption will be required, as will replacement of higher salt foods with lower salt versions. This will require increased collaboration of the food industry with public health officials, and a broad spectrum of additional research. The latter includes research to develop reduced sodium food products that maintain flavor, texture, consumer acceptability, and low cost. Such efforts will require the collaboration of food scientists, food manufacturers, behavioral scientists, and public health officials.

In reviewing the literature, gaps have been identified and the following are recommendations for additional research:

- Development of public health strategies to achieve and sustain a reduced sodium and increased potassium intake in the general population, including behavioral change studies in individuals, and community-based intervention studies.
- Development of alternative processing technologies to reduce the sodium content of foods, with a special emphasis on maintaining flavor, texture, consumer acceptability, safety, and low cost.
- Assessment of the feasibility of a large-scale, long-term clinical trial designed to assess the impact of sodium reduction on clinical cardiovascular outcomes.
- Main and interactive effects of sodium and potassium intake on noncardiovascular clinical outcomes, specifically bone mineral density, osteoporosis, and kidney disease progression.
- Assessment of genetic and dietary factors that affect salt sensitivity.
- Assessment of the clinical relevance of sodium-induced changes in plasma renin activity.
- Main and interactive effects of sodium and potassium intake on plasma renin activity.
- Main and interactive effects of sodium and potassium intake on insulin resistance.
- Development of practical tools to measure intakes of sodium and potassium and to assess total body levels of sodium and potassium.
- Development of practical tools to define and measure salt sensitivity.
- Better characterization of salt sensitivity as a phenotype and determination of its relationship to cardiovascular outcomes.
- Influence of sodium intake during infancy and childhood on blood pressure later in life.
- Main and interactive effects of sodium and potassium intake on the age-related rise in blood pressure.

- Sodium and potassium balance studies to provide estimates of electrolyte loss (sweat concentrations and total sweat loss) by physical activity level, climatic conditions, and dietary electrolyte intake in broad populations.
- Sodium and potassium balance studies during pregnancy.

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7
Sulfate

SUMMARY

Inorganic sulfate (SO_4^{2-}) is required for the synthesis of 3′-phosphoadenosine-5′-phosphosulfate (PAPS). PAPS is required for synthesis of many important sulfur-containing compounds, such as chondroitin sulfate and cerebroside sulfate. While significant levels of sulfate are found in foods and various sources of drinking water, the major source of inorganic sulfate for humans is from biodegradation due to body protein turnover of the sulfur amino acids methionine and cysteine. Dietary sulfate in food and water, together with sulfate derived from methionine and cysteine found in dietary protein and the cysteine component of glutathione, provides sulfate for use in PAPS biosynthesis. Sulfate requirements are thus met when intakes include recommended levels of sulfur amino acids. For this reason, neither an Estimated Average Requirement (and thus a Recommended Dietary Allowance) nor an Adequate Intake for sulfate is established.

Adverse effects have been noted in individuals whose drinking water source contains high levels of inorganic sulfate. Osmotic diarrhea resulting from unabsorbed sulfate has been described and may be of particular concern in infants consuming fluids derived from water sources with high levels of sulfate. Some association between increased hydrogen sulfide production and risk of ulcerative colitis has been noted as well, but has not been adequately evaluated. Overall, there is insufficient information available to set a Tolerable Upper Intake Level for sulfate.

BACKGROUND INFORMATION

Sulfur is the 14th most abundant element in the earth's crust. Sulfate is produced in the environment from the oxidation of elemental sulfur, sulfide minerals, or organic sulfur. Soils are thought to average 850 mg of sulfate/kg and sea water 885 mg of sulfate/L (Field, 1972). Industrial sulfate results from the burning of sulfur-containing fossil fuels, household wastes (e.g., detergents), and effluents from tanneries, steel mills, sulfate-pulp mills, and textile plants. Sulfuric acid accounts for an estimated 80 percent of commercial sulfur production (NRC, 1980). Additionally, thousands of tons of sulfate compounds are produced each year; annual production of sodium sulfate was estimated at 792 tons in 1987 (EPA, 1990).

Most public water supplies contain sulfate concentrations of less than 500 mg/L (EPA, 2001). Sulfate levels in water around 250 mg/L and above are detectable due to an off odor and taste, and this generally causes those exposed to water with higher concentrations of sulfate to switch to bottled water sources for drinking. Still, adaptation to water with a high sulfate content is known to occur. Extremely high sulfate concentrations in water have been recorded; for example, 1,500 mg/L in a coal mine in Pennsylvania and 63,000 mg/L in a zinc mine in Idaho (Moore, 1991).

Sulfur dioxide (SO_2) emissions represent a growing concern for industrialized countries. Sulfur dioxide in the air can react with atmospheric water to produce sulfuric acid, resulting in acid rain (Drever, 1988). This can lead to increased soil acidity and elevated levels of sulfate in ground water (Drever, 1988). Moore (1991) estimated that global SO_2 emissions have more than doubled over the last 50 years.

Sulfate improves growth in farm animals consuming diets deficient in sulfur amino acids and very low in sulfate. Thus sulfate salts are sometimes used as growth-promoting feed additives for chickens, turkeys, and pigs.

Function

Sulfate is produced in the body from the transsulfuration of methionine to cysteine, followed by the oxidation of cysteine to pyruvate and inorganic sulfate. These processes occur as a result of protein turnover, as well as from degradation of excess protein-derived methionine or cysteine. Inorganic sulfate also results from the metabolism of several organic and inorganic sulfur compounds present

in food and water. Glutathione, an important antioxidant compound, is one of the more studied nonprotein organic sources of sulfate in the diet.

There are hundreds of sulfur-containing compounds in the human body, and the body synthesizes all of them, with the exception of the vitamins thiamin and biotin. Precursors include sulfate obtained from dietary intake and ingestion of the indispensable amino acids methionine and cysteine (cysteine is considered conditionally indispensable) (Shils et al., 1999).

One of the important roles for sulfate is in the biosynthesis of 3′-phosphoadenosine-5′-phosphosulfate (PAPS). Inorganic sulfate is required along with adenosine triphosphate. PAPS, also known as active sulfate, is used in the biosynthesis of many essential body compounds (Box 7-1), some of which are not absorbed intact when present in foods.

Physiology of Absorption and Metabolism

Gastrointestinal absorption of sulfate can occur in the stomach, small intestine, and colon (Anast et al., 1965; Batt, 1969; Cardin and Mason, 1975, 1976; Cole and Evrovski, 2000; Kandylis, 1983; Kaneko-Mohammed and Hogben, 1964). Absorption is a sodium-dependent active process (Ahearn and Murer, 1984; Florin et al., 1991; Langridge-Smith et al., 1983). When soluble sulfate salts (e.g., potassium sulfate or sodium sulfate) are consumed, more than 80 percent of oral sulfate doses are absorbed, as shown by isotopic tracer studies (Bauer, 1976; Florin et al., 1991).

With insoluble sulfate salts, such as barium sulfate, almost no absorption occurs (Ahmed and Hamza, 1989). When magnesium sul-

BOX 7-1 Examples of Compounds Biosynthesized Using 3′-Phosphoadenosine-5′-Phosphosulfate

- Chondroitin sulfate
- Dermatan sulfate
- Keratan sulfate
- Heparan sulfate
- Cerebroside sulfate
- Tyrosine-o-sulfate
- Taurolithocholate sulfate (bile salt)
- Estrone 3-sulfate

fate is used to promote osmotic diarrhea, sulfate absorption is inversely proportional to the extent of the osmotic effect. Sulfate that is not absorbed in the upper gastrointestinal tract passes to the large intestine and colon, where it is either excreted in the feces, reabsorbed, or reduced by anaerobic bacteria to metabolites, such as hydrogen sulfide (Pitcher and Cummings, 1996; Roediger et al., 1997).

Because the majority of body sulfate is obtained from the ingestion of protein-derived methionine and cysteine and because the primary route of sulfate excretion is in the urine, 24-hour urinary sulfate excretion is strongly correlated with 24-hour urinary excretion of urea, the end product of dietary protein metabolism (Greer et al., 1986; Houterman et al., 1997; Sabry et al., 1965). Urinary sulfate excretion has recently been suggested as a measure of sulfur amino acid metabolism in humans (Hamadeh and Hoffer, 2001; Hoffer, 2002).

If one assumes that adults whose dietary protein needs are being met will consume a daily intake of 2 g of methionine and 2 g of cysteine, an equal amount of methionine and cysteine would be oxidized, producing 960 mg of sulfur, or 2.8 g/day of inorganic sulfate. A daily intake of inorganic sulfate as high as 1.3 g/day can be obtained from water and other beverages (0.5 g/L × 2.6 L/day). A quantity of sulfate greater than this amount would likely be produced daily from metabolism of methionine and cysteine in food plus that derived from body protein turnover. An analysis of the sulfate content of various diets using foods purchased at supermarkets suggests a large variation in daily inorganic sulfate intake, ranging from 0.2 to 1.5 g (2.1–15.8 mmol)/day[1] (Florin et al., 1991). Metabolism of organic sulfur compounds, such as methionine and cysteine, supplies over half of the sulfate; the remainder is supplied from preformed sulfate in water and foods (see Table 7-1).

Clinical Effects of Inadequate Intake

Extensive work with laboratory animals has shown that growth is stunted when dietary sulfate is purposely eliminated from both the food and water supply and when sulfur amino acids, particularly cysteine, are provided at levels resulting in deficiency signs. Importantly, the addition of sulfate to these deficient diets resulted in

[1] To convert mmol of sulfate to mg of sulfate, multiply mmol by 96.1 (the molecular weight of sulfate).

TABLE 7-1 Estimated Total Daily Intake of Sulfate

Source	Concentration in Source per g (mmol) of Sulfur Amino Acid	Daily Intake of Source	Daily Amount, g/d (mmol/d)
Dietary organic sulfur containing compounds (includes methionine and cysteine)	0.7 (7.3)	Average protein intake reported in NHANES III[a] is ≈ 100 g/d, which provides ≈ 4 g of sulfur amino acids	2.8 (29)
Sulfate in drinking water and beverages	0.1–0.5 g/L (1.0–5.2 mmol/L) of fluid	2.6 L[b]	0.26–1.3 (2.7–13) Average = 0.78 (7.8)
Inorganic sulfate in food	Varies	2–3 kg	0.2–1.5 (2.1–15.8) Average = 0.85 (8.8)
Estimated total sulfate			3.25–5.55 (33.8–57.8) Average = 4.40 (45.8)

[a] Third National Health and Nutrition Examination Survey.
[b] Estimated intake of drinking water and beverages for men and women from Chapter 4.

significant growth responses (Anderson et al., 1975; Byington et al., 1972; Gordon and Sizer, 1955; Machlin and Pearson, 1956; Sasse and Baker, 1974a, 1974b; Smith, 1973; Soares, 1974). In young animals, a minimal level of 165 to 200 mg of sulfate/kg of diet has been found to yield a maximal growth response in rats (Smith, 1973) or chicks (Sasse and Baker, 1974b) fed a diet limited in cysteine.

Using similar dietary conditions in adult men (low sulfate, sulfur amino acid-deficient diet), nitrogen retention increased when sodium sulfate was added to the diet in an amount equivalent to that provided by additional methionine (Zezulka and Calloway, 1976).

Under these conditions, sulfate is probably used directly for PAPS biosynthesis, thereby sparing cysteine such that more of the cysteine is made available for protein synthesis and growth. A recent study in which lower levels of serum sulfate were detected when acetaminophen was given with glucosamine sulfate to normal adults

provides additional support for a role of nonprotein sulfate in sulfation and metabolism of phenolic compounds (Hoffer et al., 2001). In humans, sulfate ingestion would almost always exceed 3 g/day as a result of sulfate ingestion in food and water, together with the sulfate produced in the body from metabolism.

INDICATORS CONSIDERED FOR ESTIMATING THE REQUIREMENT FOR SULFATE

Growth responses in chicks and rats occur when sulfate is added to low-sulfate diets that are deficient in cysteine (Byington et al., 1972; Sasse and Baker, 1974b); nitrogen retention is improved in humans placed under a similar dietary regimen (Zezulka and Calloway, 1976). Whether sulfate incorporation into 3′-phosphoadenosine-5′-phosphosulfate (PAPS), or whether PAPS synthase activity could be used as a measure of sulfate adequacy, is not known. The one human study conducted to date did not attempt to measure these parameters (Zezulka and Calloway, 1976). Because sulfate is an obligatory end product of sulfur amino acid turnover, inadequate sulfate consumption (or production) is unlikely to occur in any setting other than where protein deficiency is also present.

FACTORS AFFECTING SULFATE REQUIREMENTS

Limited information is available on the extent to which 3′-phosphoadenosine-5′-phosphosulfate (PAPS) biosynthesis can be affected by available inorganic sulfate. Whether increased amounts of PAPS are needed in diseases, such as arthritis, in which sulfated compounds (e.g., sulfates of glucosamine and chondroitin) are implicated is unknown because in most studies sufficient sulfur amino acids are provided as part of dietary protein (Hoffer et al., 2001). The primary factor affecting a dietary need for sulfate is the extent to which sulfur-containing compounds are available for degradation to provide sulfate for PAPS biosynthesis. Unlike most other nutrients, the body's need for sulfate can be met by consuming other required nutrients, sulfur amino acids. Thus a deficiency of sulfate is not found in humans consuming normal protein intakes with adequate sulfur amino acids. Ingestion of methionine, cysteine, and glutathione in foods, along with consumption of other sulfated compounds in both food and beverages, is sufficient to meet the body's requirement for sulfate.

Sulfate requirements for the growing fetus are high (Cole and

Evrovski, 2000; Cole et al., 1992), and this raises questions concerning sulfate requirements during pregnancy, particularly in situations where the mother is on a medication, such as acetaminophen, that is known to deplete sulfate (Morris and Levy, 1983).

FINDINGS BY LIFE STAGE AND GENDER GROUP

Sulfate intake (as well as sulfate produced via amino acid turnover) typically exceeds the need for 3′-phosphoadenosine-5′-phosphosulfate biosynthesis, as evidenced by maintenance of normal levels of urinary excretion of sulfate (Cole and Evrovski, 2000) when sulfur amino acids are adequate. Recommended intakes have already been established for sulfur amino acids, which would thus cover the need for inorganic sulfate (IOM, 2002/2005). Given these two points, neither an Estimated Average Requirement (and thus a Recommended Dietary Allowance) nor an Adequate Intake for sulfate is established.

INTAKE OF SULFATE

Sources

Approximately 19 percent of total sulfate comes from ingested inorganic sulfate from foods and 17 percent of total comes from inorganic sulfate in drinking water and beverages (Table 7-1). Many other sulfur compounds in food can yield inorganic sulfate as a result of degradation or turnover. Among organic compounds, methionine and cysteine in food proteins, glutathione in both animal and vegetable products (Wierzbicka et al., 1989), taurine in animal-source foods, lanthionine (a cross-linked sulfur amino acid produced when protein-bound cysteine undergoes heat treatment at an alkaline pH), and sulfated glycosaminoglycans in both plant- and animal-derived foods are important contributors of organic sulfate, providing the remaining approximately 64 percent of total sulfate available for body needs.

Other organic sulfur compounds are ingested in certain situations. Several drugs contain sulfur, and several cysteine derivatives are used in certain clinical situations. For example, N-acetyl-L-cysteine is used as a mucolytic agent for treating sepsis, respiratory diseases, and various autoimmune deficiency diseases (Baker and Wood, 1992; Kelly, 1998). Sulfur-containing D-penicillamine or dimercaptopropanol is used for treating the copper toxicity problems seen in Wilson's disease (Smithgall, 1985). Also, small quanti-

ties of S-methylmethionine are present in many foods (Kovatscheva and Popova, 1977). Some individuals self-medicate with sulfur-containing compounds, such as chondroitin sulfate, glucosamine sulfate, and methylsulfonylmethane, for a possible benefit to bones and joints. Evidence has been presented suggesting that the beneficial effects of glucosamine sulfate for osteoarthritis may be due more to the sulfate than to the glucosamine contained in this compound (Hoffer et al., 2001).

The sulfate content of a few foods and beverages has been estimated (Tables 7-2 and 7-3) by Florin et al. (1993). Their analytical procedures involved acid hydrolysis; thus their sulfate values were referred to as "available" sulfate and would include not only free anionic sulfate, but also that liberated from various ester sulfates, such as amino sulfonates (e.g., heparin), nitric oxide-sulfonates (e.g., glucosinolates), phospho-sulfonates (e.g., 3′-phosphoadenosine-5′-phosphosulfate), sulfuryl-sulfonates (e.g., cysteine sulfosulfate), and oxy-sulfonates (e.g., mucin and sulfate-conjugated bile acids, but not carbo-sulfonates (e.g., taurine). Thus the methodology was designed to mimic the digestive process in-

TABLE 7-2 Sulfate Content of Selected Foods

Food	Number of Samples	Mean Sulfate Content, mg/g (standard deviation)
Almonds	4	0.9 (0.61)
Bread, commercial brown wheat	14	1.5 (0.46)
Bread, commercial white	6	1.3 (0.31)
Broccoli	4	0.9 (0.69)
Brussels sprouts	3	0.9 (0.085)
Cabbage	4	0.8 (0.078)
Cauliflower	4	0.5 (0.41)
Dates	4	1.1 (0.54)
Dried apples	3	4.9 (0.4)
Dried apricots	2	3.0 (1.5)
Dried potato	4	2.0 (0.74)
Flour, soya	3	1.2 (0.25)
Pasta, durum wheat	3	0.3 (0.25)
Peanuts	4	0.7 (0.16)
Prunes	2	1.0 (1.2)
Raisins	4	1.3 (0.29)
Sausage, English style	3	1.0 (0.11)
Sunflower seeds	3	0.6 (0.075)

SOURCE: Florin et al. (1993).

TABLE 7-3 Sulfate Content of Selected Beverages

Beverage	Number of Samples	Sulfate Content, Mean (mg/L)
Beer, bitter	7	260 (64)
Beer, lager	4	130 (33)
Cider	3	270 (60)
Coconut milk	4	500 (160)
Cola	4	80 (66)
Juice, apple	6	70 (13)
Juice, grape (red, white)	4	200 (110)
Juice, tomato	3	250 (170)
Milk, cow	4	100 (18)
Milk, human[a]	38	5 (0.9)
Milk, infant formula[a]	16	66 (9)
Wine, red	8	380 (90)
Wine, white	6	300 (110)

[a] From Hoppe et al. (1998).
SOURCE: Florin et al. (1993).

volving gastric acid and intestinal and bacterial enzymes that release sulfate from sulfate esters in food.

A wide range of "available" sulfate values were estimated from different foods, but particularly high levels (> 1 mg/g) were found in some fruits, soya flour, certain breads, and sausages. Among beverages, several juices, beers, wines, and ciders were found to contain more than 250 mg of sulfate per L. Among inorganic sulfur sources in the food and water supply, sulfate itself, along with sulfite (SO_3^{2-}), predominate, the latter being a food additive that functions as a preservative. Sulfite can also occur naturally as a consequence of fermentation (e.g., in wine). Sulfite is easily oxidized to sulfate, either in food itself or in the gut following consumption. Moreover, sulfite, as well as other inorganic sulfur compounds in the +4 valence state (e.g., SO_2, HSO_3^{1-}) are highly bioactive and have well-known toxic side effects (Til and Feron, 1992; Wedzicha, 1992).

Sulfate ingestion from drinking water is highly variable and depends on the area of the country from which the water is obtained. Some well water in rural areas of the United States has been known to contain upwards of 500 mg/L (Moore, 1952), and some of the "mineral" waters sold with health claims have been reported to exceed this level (Allen et al., 1989). Distilled water contains very little, if any, sulfate, and deionized water contains no sulfate.

Human milk is very low in sulfate (5 mg/L), and even though an average value for infant formula products (both milk- and soy-based) was found to be 13 times higher than that in human milk (66 mg/L), these levels of sulfate are still lower than those in many sources of drinking water (Hoppe et al., 1998).

Intake

Surveys of sulfate intake from food and beverages are currently not available. The Third National Health and Nutrition Examination Survey has not estimated sulfate intake directly. Indirect estimates of sulfate intake can be calculated from the intakes of sulfur-containing amino acids. Table 7-4 provides estimates of sulfate intake that would be derived from metabolism of cysteine and methionine. The estimates provided in the table thus do not include sulfate from food, beverages, or drinking water, nor that derived from organic sulfur compounds other than methionine and cysteine.

ADVERSE EFFECTS OF OVERCONSUMPTION

Hazard Identification

Diarrhea

Adult Human Data. Osmotic diarrhea and loose stools have been reported with high intakes of sulfate consumed in water (Backer, 2000). Such adverse effects are usually short term, but they may be more severe in infants. The U.S. Environmental Protection Agency (EPA) and the Centers for Disease Control and Prevention (CDC) collaborated in a 1997 study to determine whether high levels of sulfate in drinking water would cause diarrhea or other gastrointestinal disturbances in infants and in adults categorized as "transients" (i.e., those experiencing an abrupt change in water sulfate concentration from low to high) (EPA, 1999a). The study involved 105 adult volunteers from Atlanta, Georgia, including CDC and EPA employees, who were randomly assigned to one of five possible sulfate exposure groups. Sulfate concentrations (from sodium sulfate) tested in drinking water were 0, 250, 500, 800, and 1,200 mg/L. Participants were given water for 6 days. The water provided for days 1, 2, and 6 of the 6-day study contained no added sulfate, whereas the water provided for days 3, 4, and 5 contained added

TABLE 7-4 Mean and Percentiles of Sulfate (g) Derived from the Usual Daily Intake of Sulfur-Containing Amino Acids

Sex/Age Category[a]	*n*	Mean	Percentile	
			1st	5th
Both sexes, 2–6 mo	793	0.41	0.14	0.21
Both sexes, 7–12 mo	827	0.76	0.21	0.21
Both sexes, 1–3 yr	3,309	1.24	0.28	0.49
Both sexes, 4–8 yr	3,448	1.58	0.90	1.07
M, 9–13 yr	1,219	2.07	1.15	1.37
M, 14–18 yr	909	2.53	1.21	1.53
M, 19–30 yr	1,902	2.78	1.58	1.88
M, 31–50 yr	2,533	2.56	1.31	1.61
M, 51–70 yr	1,942	2.22	0.90	1.20
M, 71+ yr	1,255	1.85	0.81	1.04
F, 9–13 yr	1,216	1.66	1.25	1.36
F, 14–18 yr	949	1.59	0.58	0.83
F, 19–30 yr	1,901	1.71	0.92	1.11
F, 31–50 yr	2,939	1.72	0.98	1.16
F, 51–70 yr	2,065	1.55	0.72	0.92
F, 71+ yr	1,368	1.40	0.64	0.83
Pregnant	346	2.07	1.22	1.44
Lactating	99	2.45	1.71	1.92
P/L	440	2.16	1.30	1.51
All individuals	28,575	1.94	0.74	0.99
All individuals (+P/L)	29,015	1.95	0.76	1.01

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Sulfate content calculated using 0.7 g sulfate/g of sulfur amino acid from the Third National Health and Nutrition Examination Survey (1988–1994) intake data for cysteine and methionine.

DATA SOURCE: IOM (2002/2005).

sulfate. While the study did not indicate how much water was consumed, nor the season of the study, there were no statistically significant differences in the number of bowel movements for days 1, 2, and 6 compared with those for days 3, 4, and 5. In regression analyses of diarrhea frequency by sulfate dose (dose/kg of body weight), sulfate intake was not a significant predictor of diarrhea.

Evaluation of data from 248 private wells in North Dakota indicated that 62 percent of consumers experienced a laxative effect when the sulfate concentration in the well water exceeded 1,000 mg/L (Moore, 1952). Two studies in healthy adults were reported by Heizer and colleagues (1997). Four participants in the dose-

10th	25th	50th	75th	90th	95th	99th
0.21	0.28	0.35	0.49	0.70	0.77	1.33
0.35	0.49	0.70	0.98	1.33	1.54	2.03
0.63	0.91	1.19	1.54	1.96	2.17	2.80
1.16	1.34	1.55	1.79	2.02	2.17	2.48
1.51	1.74	2.02	2.37	2.70	2.91	3.36
1.71	2.04	2.46	2.95	3.43	3.73	4.37
2.05	2.36	2.74	3.15	3.58	3.84	4.41
1.79	2.11	2.49	2.93	3.40	3.70	4.33
1.39	1.72	2.13	2.62	3.16	3.56	4.45
1.20	1.45	1.78	2.16	2.58	2.88	3.54
1.42	1.53	1.65	1.79	1.90	1.98	2.14
0.97	1.22	1.53	1.90	2.29	2.55	3.11
1.22	1.41	1.68	1.97	2.25	2.43	2.82
1.27	1.46	1.69	1.94	2.20	2.37	2.71
1.04	1.25	1.51	1.81	2.11	2.31	2.74
0.94	1.13	1.37	1.63	1.90	2.09	2.47
1.55	1.77	2.04	2.32	2.62	2.81	3.18
2.03	2.23	2.44	2.67	2.88	3.01	3.26
1.65	1.86	2.13	2.43	2.70	2.88	3.23
1.15	1.45	1.85	2.33	2.84	3.18	3.91
1.16	1.46	1.86	2.33	2.84	3.18	3.90

ranging study were given six sulfate doses (in water) of 0, 400, 600, 800, 1,000, or 1,200 mg/L for six consecutive 2-day periods, while six other subjects in a single-dose study received sulfate doses (in water) of 0 and 1,200 mg/L for two consecutive 6-day periods. In the dose-ranging study, the mean sulfate intake coming from drinking water in the 1,200 mg/L group was 2.7 g, while the mean sulfate intake in drinking water in the single-dose study at 1,200 mg/L was 2.9 g due to differences in total water consumed. In both studies at the 1,200-mg/L sulfate dose, a small increase in stool mass occurred, but no complaints of diarrhea or changes in stool frequency were reported.

Severe diarrhea in five healthy men was reported when they were given 8 g of sodium sulfate (6.7 g of sulfate) as a single dose; however, little or no diarrhea occurred when divided into four equal hourly doses (Cocchetto and Levy, 1981).

Magnesium salts have been prescribed as a cathartic. Although magnesium hydroxide and magnesium oxide are the primary salts utilized for this purpose, magnesium sulfate (Epsom salts) is also used. These poorly absorbed ions exert an osmotic effect in the intestinal lumen and cause water to be retained, thus increasing the fluidity of the intraluminal contents (Izzo et al., 1996). High oral doses of magnesium sulfate can lead to severe magnesium toxicity in patients with impaired renal function, but toxicity is uncommon in healthy individuals (Mordes, 1978). The bioavailability of magnesium was examined following a large oral dose of 13.9 g (56.5 mmol) of magnesium sulfate over a 4-hour period in six men (Morris et al., 1987). All subjects experienced mild to moderate diarrhea. While the magnesium was poorly absorbed (only 6.9 percent of the oral dose was absorbed by 72 hours), approximately 38 percent of sulfate appeared in the urine. The comparatively poor absorption of magnesium thus may be the primary ion responsible for the diarrhea seen since absorption of sulfate was much greater.

TABLE 7-5 Case Reports of Infants Exposed to High Levels of Sulfate

Subject	Sulfate in Water Supply (mg/L)	Median Weight[a] (kg)	Water Intake[b] (mL/d)	Sulfate Dose (mg/kg)	Sulfate Dose (mg/d)
5-mo-old boy	630	7.3	848	73	534
10-mo-old boy	720	9.7	896[c]	66	645
1-yr-old girl	1,150	9.5	906	110	1,042

[a] Median weights from Kuczmarski et al. (2000).

[b] Fiftieth percentile of daily intake of drinking and beverage water (Appendix Table D-3).

Infant Human Data. A number of studies have been conducted in human infants and very young animals because of their vulnerability to the adverse consequences of osmotic diarrhea. One study of 274 infants aged 6.5 to 30 weeks in 19 South Dakota counties involved data on frequency of diarrhea (Esteban et al., 1997). One hundred seventy households participating in the study also submitted water samples. The median sulfate level of the water samples was 264 mg/L. In approximately 83 percent of the households that submitted water samples, no significant association was found between sulfate ingestion and the reported incidence of diarrhea. The median sulfate concentration of water samples and the mean daily sulfate intake for infants who did not develop diarrhea were 258 mg/L and 29 mg/kg/day, respectively. For infants who developed diarrhea, the median water sulfate concentration was 289 mg/L, and the mean daily sulfate intake was 28 mg/kg/day. At least one small case-history study suggested that infants exposed to water sulfate concentrations above 600 mg/L may develop diarrhea (see Table 7-5) (Chien et al., 1968).

Pregnant Animal Data. Only one study of the effect of sulfate on animals during pregnancy was found. In a swine study, water con-

Comments
Developed frequent green and watery stools promptly after consuming formula made with well water; prior to consumption, the infant tended to be constipated
Developed watery brown stools promptly after consuming formula made with well water; stools contained no bacterial pathogens, ova, or parasites
Developed persistent diarrhea after several days of consuming well water; parents and two siblings developed intermittent diarrhea after consuming well water for 1 wk; stools contained no bacterial pathogens, ova, or parasites

[c] Mean of daily intake of drinking and beverage water for infants and children 7–12 mo and 1–3 yr of age (Appendix Table D-3).

SOURCE: Chien et al. (1968).

taining 320, 1,800, or 3,300 mg/L of sulfate (as sodium sulfate) was provided to sows during the last 84 days of gestation and throughout a 28-day lactation period (Paterson et al., 1979). No effects on stool consistency were apparent in either sows or first-litter gilts.

Pregnant Human Data. Magnesium sulfate is administered parenterally in various clinical situations, particularly as a preventative measure for eclampsia during pregnancy. Although deemed to be safe and effective, Ricci and coworkers (1990) observed that serum sulfate concentration increased approximately twofold in 11 pregnant women treated with magnesium sulfate.

Young Animal Data. A sulfate dose-response study in neonatal artificially reared piglets added doses of sulfate (from sodium sulfate) to the liquid diet ranging from 0 to 2,200 mg/L (0 to ≈2,640 mg/kg of body weight)/day (Gomez et al., 1995). The basal diet contained 270 mg/L (≈325 mg/kg)/day of sulfate from dietary ingredients (deionized water was used to prepare the liquid diets). While neither growth rate nor voluntary dietary intake during the 18-day study was affected by sulfate dose, nonpathogenic diarrhea became evident at sulfate concentrations greater than 1,200 mg/L (based on an estimated water intake of ≈1,440 mg/kg/day). Diarrhea occurred in 50 percent of the piglets receiving 1,600 to 1,800 mg/L (≈1,920 to 2,160 mg/kg)/day, and in all piglets receiving 2,000 to 2,200 mg/L (≈2,400 to 2,640 mg/kg)/day of supplemental sulfate. Urinary sulfate reached a maximum concentration at 1,600 mg/L (≈1,920 mg/kg)/day of oral sulfate supplementation. From these data it was inferred that sulfate at an intake above 1,600 mg/L (≈1,920 mg/kg)/day was osmotically active due to malabsorption.

Sulfate-supplemented water was also provided to piglets for a longer time period, from 28 days of age (weaning) to 56 days of age; the sulfate concentration was 3,000 mg/L (based on estimated water intake, ≈354 to 378 mg/kg body weight/day) provided as sodium sulfate or as a 1:1 mixture of sodium sulfate and magnesium sulfate (Paterson et al., 1979). Fecal scoring indicated that both sulfate regimens resulted in a higher incidence of loose stools and intermittent diarrhea compared with the control piglets.

Acidosis

Metabolic acidosis has been shown to result from consumption of "flowers of sulfur," a fine, yellow powder that is more than 99.5 percent pure sulfur (Blum and Coe, 1977; Schwartz et al., 1986).

Magnesium sulfate is given intravenously in various clinical situations, particularly to prevent eclampsia during pregnancy. Although deemed to be safe and effective when used in this therapeutic mode, serum sulfate concentration was increased approximately twofold in 11 pregnant women treated with magnesium sulfate (Ricci et al., 1990). No reports of acidosis as the result of consuming the dietary supplement chondroitin sulfate were found.

Ulcerative Colitis

Sulfate and undigested sulfur compounds have been implicated in the etiology of ulcerative colitis (Magee et al., 2000; Pitcher and Cummings, 1996; Roediger et al., 1997). The specific agent is thought to be hydrogen sulfide, which is produced in the colon from sulfate by sulfate-reducing bacteria. Sulfate-reducing bacteria use either sulfate or sulfite as a terminal electron acceptor, releasing sulfide into the lumen where it is converted to hydrogen sulfide gas (H_2S) (Pitcher and Cummings, 1996). It is now clear that sulfate can also enter the colon from unabsorbed dietary sulfate as well as from unabsorbed sulfur amino acids, taurine, and sulfur-containing food additives (e.g., sulfur dioxide, sulfites, and carrageenan). A portion of the sulfate produced from amino-acid turnover can also reenter the gut from the circulation (Garcia and Stipanuk, 1992). Excess luminal sulfide is thought to overburden mucosal detoxification systems, resulting in impaired butyrate oxidation and colonic epithelial inflammation.

Sodium sulfate supplementation has been demonstrated to inhibit methaneogenesis and stimulate the growth of sulfate-reducing bacteria in the colon of humans (Christl et al., 1992). Experimentally, colitis has been produced in Guinea pigs and rabbits that were given degraded carrageenan, sodium lignosulfate, or sulfated amylopectin in their drinking water (Marcus and Watt, 1969, 1974). It was also produced in rats, mice, and hamsters by administration of dextran sulfate sodium (Carrier et al., 2002; Ohkusa, 1985; Okayasu et al., 1990).

Among the amino acids in protein, cysteine and cystine are well known to be among the poorest absorbed from the upper small intestine (NRC, 1994). Heat treatment of proteins contributes to the poor digestibility of cysteine because heating protein causes cysteine to be oxidized to cystine, a dimer that is poorly absorbed (Miller et al., 2001; Parsons et al., 1992).

These observations, together with the fact that fecal sulfide levels are elevated in ulcerative colitis patients (Florin et al., 1990; Pitcher

et al., 1995), add credence to the link between colonic sulfide levels and ulcerative colitis. Indeed, drug therapy involving 5-aminosalicylic acid (Pitcher et al., 1995; Roediger and Duncan, 1996) and gentamycin (Pitcher et al., 1994) for ulcerative colitis is known to suppress hydrogen sulfide production. Moreover, standard therapy for ulcerative colitis patients has included restriction of foods, such as milk, eggs, and cheese, that are significant sources of dietary sulfur (Truelove, 1961). More recently, dextran sulfate sodium-induced ulcerative colitis in rats was shown to be exacerbated by dietary iron supplementation, a potent oxidant, but was ameliorated by vitamin E supplementation (Carrier et al., 2002). However, vitamin E supplementation did not affect oxidative stress, as measured by plasma and colonic lipid peroxides and glutathione peroxidase activity, thus suggesting another mechanism for reducing inflammation.

Dose-Response Assessment

Adults

Adverse effects that have been associated with sulfate ingestion include osmotic diarrhea and ulcerative colitis. Generally, a self-regulating effect occurs in that higher concentrations of water sulfate have an odor and off taste, which causes those exposed to water with a high sulfate content to use bottled water. Mineral water sources, however, can vary widely in both cation and anion concentration. Nonetheless, studies have shown that both demineralized bottled water and spring bottled water contain sulfate levels below 500 mg/L, with most lower than 250 mg/L (Allen et al., 1989; Ikem et al., 2002).

Short-term exposure (3 days) to sulfate levels in water (concentration 1,200 mg/L, which would lead to ingestion of 3.6 g of sulfate based on the median intake of water for 19- to 30-year-old men of 3 L/day [Appendix D]), did not induce noticeable diarrhea in the CDC/EPA study in healthy adults (EPA, 1999a). Regression analysis of diarrhea frequency by sulfate dose (dose/kg of body weight) found that sulfate dose was not a significant predictor of diarrhea (EPA, 1999a). Longer-term studies of 6 days in six healthy men showed little change at 2.9 g (1,200 mg/L)/day as well (Heizer et al., 1997). Severe diarrhea has been noted when 6.7 g of sulfate was given in a single dose, but was absent when provided in four divided doses (Cocchetto and Levy, 1981).

As described in the previous section, evidence on the role of sulfate in the etiology of ulcerative colitis is inconclusive. Also, available data make it difficult to rule out other factors that might be causative of colitis exacerbations. Hence it is not possible to identify a Tolerable Upper Intake Level (UL) for sulfate based either on diarrhea or on a possible role in ulcerative colitis.

Infants

In one study of infants, the reported occurrence of osmotic diarrhea did not vary by estimated intake of sulfate (Esteban et al., 1997). Those who developed diarrhea drank water with a median sulfate concentration of 289 mg/L, while those who did not have diarrhea drank water with a median sulfate concentration of 258 mg/L. Mean daily sulfate intake for infants who did not develop diarrhea was 29 mg/kg/day, while the mean daily sulfate intake of infants developing diarrhea was 28 mg/kg/day. In a small-case series, infants exposed to water sulfate concentrations above 600 mg/L (estimated intake about 66 mg/kg) did develop diarrhea (Chien et al., 1968).

Animal dose-response data using neonatal piglets may be relevant to infants. The study of Gomez and coworkers (1995) included doses of sulfate (from sodium sulfate) ranging from 0 to 2,200 mg/L (0 to 2,640 mg/kg of body weight/day) added to a liquid diet of 270 mg/L (≈325 mg/kg/day of sulfate in the basal diet). Nonpathogenic diarrhea became evident at sulfate concentrations greater than 1,200 mg/L (≈1,440 mg/kg)/day. Diarrhea occurred in 50 percent of the piglets receiving 1,600 to 1,800 mg/L (≈1,920 to 2,160 mg/kg)/day, and in all piglets receiving 2,000 to 2,200 mg/L (≈2,400 to 2,640 mg/kg)/day of supplemental sulfate.

Based on this study, a sulfate intake of up to 1,470 mg/L (amount/kg added + background = 1,200 + 270) did not lead to diarrhea. This level is equivalent to approximately 1,530 mg (1,470 × 1.04 L)/day of sulfate (the piglets consumed a liquid diet containing 20 percent dry matter; 3.76 kg of dry matter was consumed over an 18-day feeding period, therefore piglets consumed on average 1.04 kg/day [(3.76 ÷ 0.2) ÷ 18 days] assuming that the density of the formula given was approximately 1 kg/L).

Overall, data are inadequate to set a UL for sulfate for infants. Based on neonatal piglet data, however, it would appear that levels exceeding 1,500 mg/day may cause some degree of diarrhea.

Special Considerations

Renal Failure. Increased serum sulfate levels are a common feature of kidney failure. Levels of serum sulfate may be elevated 7 to 24 times the normal level in an individual with acute renal failure. In end-stage renal disease, hemodialysis and peritoneal dialysis treatment remove sulfate, but serum sulfate levels are often still elevated (Cole and Evrovski, 2000; Holmes et al., 1960; Kirschbaum, 1998). Increased serum sulfate concentration results in increased complexation with calcium, and this may in part be responsible for the parathyroid stimulation that occurs in chronic renal disease (Cole and Evrovski, 2000; Michalk et al., 1981). The hypersulfatemia of chronic renal failure may directly affect the trans-sulfuration pathway and contribute to the severity of homocysteinemia typically seen in this condition (Nakanishi et al., 2002).

Hyperthyroidism. Hyperthyroidism increases basal metabolic rate which, in turn, increases protein catabolism. Increased serum sulfate levels have been noted in hyperthyroidism, probably due to increased breakdown of protein and thus sulfur amino acids (Tallgren, 1980). The implications of the hypersulfatemia associated with hyperthyroidism are unclear.

Risk Characterization

Based largely on taste considerations, the U.S. Environmental Protection Agency (EPA) recommends an upper limit of 250 mg/L for sulfate in drinking water. EPA has also recommended, but not required, that the maximum sulfate contaminant concentration be set at 500 mg/L for the prevention of acute onset of diarrhea (EPA, 2002b). This is the same maximum contaminant level as the Canadian standard (Health Canada, 2002). The maximum contaminant level sulfate standard of the World Health Organization is 400 mg/L (WHO, 1984).

The American Water Works Association has officially objected to these standards. The association's position is that if any maximum contaminant level is to be set for sulfate, it should be set at a level not less than 1,000 mg/L, and this should apply only to infants (AWWA, 1995).

In 1994, EPA estimated that 2,000 of the 54,000 public water systems in the United States had sulfate concentrations higher than 500 mg/L, and most of these occurred in systems serving populations of less than 10,000 people (EPA, 1999b). None of the public

water systems serving populations of over 100,000 people had sulfate levels that exceeded 500 mg/L. Currently, EPA has made a preliminary determination not to regulate sulfate in drinking water (EPA, 2002a).

RESEARCH RECOMMENDATIONS

- The relationship of urinary sulfate as a marker of sulfate absorption in evaluating adverse effects due to high intakes of sulfate.
- Sulfate supplementation of low-cysteine food products (e.g., casein-based enteral formula) to determine if supplementation improves growth or nitrogen balance.
- Sulfate needs during pregnancy, particularly the sulfate requirements of the growing fetus.
- Evaluation of using 3′-phosphoadenosine-5′-phosphosulfate or other biomarkers to determine dietary sulfate sufficiency.
- Better data on the relationship of diarrhea to sulfate intake in infants.
- The effects of acute versus chronic sulfate ingestion on diarrhea, as well as whether and at what point adaptation occurs.
- Survey studies comparing high versus low sulfate water ingestion from public water supplies that appropriately control for other causes of intestinal disturbances.
- Studies to evaluate whether chronic exposure to high sulfur (both cystine and sulfate) ingestion predisposes individuals to ulcerative colitis, and the role of hydrogen sulfide in its etiology.
- Studies to determine how much of the sulfate produced via turnover in metabolism reenters the bowel and thus may serve as an irritant or oxidant.
- Absorption studies using acute and chronic sulfate doses.
- Analytical studies to determine sulfate, as well as total sulfur content, of foods.

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8

Applications of Dietary Reference Intakes for Electrolytes and Water

OVERVIEW

This chapter presents a general discussion of the appropriate uses of the Dietary Reference Intakes (DRIs) in the assessment and planning of diets for individuals and for groups. It also provides guidance for the use of the DRIs developed for nutrients presented in this report, including specific examples and special considerations.

The DRIs may be used for many purposes, most of which fall into two broad categories: assessing current nutrient intakes and planning for future nutrient intakes. Each category may be further subdivided into uses related to the diet of an individual and uses related to the diets of groups (Figure 8-1).

In the past, Recommended Dietary Allowances (RDAs) in the United States and Recommended Nutrient Intakes (RNIs) in Canada were the primary reference standards available to health professionals for assessing and for planning diets of individuals and groups and for making judgments about inadequate and excessive intake. However, neither the former RDAs nor the RNIs were ideally suited for many of these purposes (IOM, 1994). The DRIs provide a more complete set of reference values. The transition from using the former RDAs and RNIs to using all of the DRIs appropriately will require time and effort by health professionals and others.

Only Adequate Intakes (AI) and, in some cases, Tolerable Upper Intake Levels (UL), have been established for the nutrients presented in this report. This chapter provides a brief description of the appropriate uses of each of the new reference value categories.

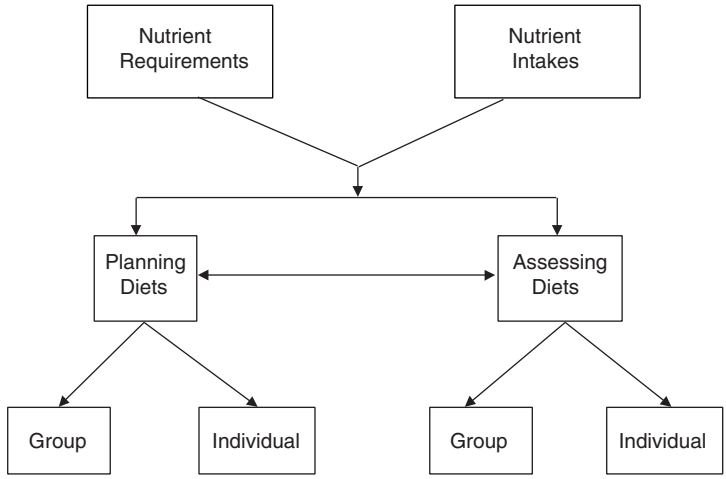

FIGURE 8-1 Conceptual framework—Uses of Dietary Reference Intakes. Nutrient intakes include all sources of nutrients: foods, beverages, and dietary supplements.

Extensive detail on the application of all of the various DRI values can be found in the reports on the application of the DRIs in assessment (IOM, 2000) and in planning (IOM, 2003).

Included in this chapter are specific applications to the nutrients discussed in this report. Details on how the DRIs are set with reference to specific life stages and gender and the criterion that defines adequacy and excess for each of these nutrients are given in Chapters 4 through 7.

ASSESSING NUTRIENT INTAKES OF INDIVIDUALS

Dietary assessment methods have several inherent inaccuracies. One is that individuals underreport their intakes (Mertz et al., 1991; Schoeller, 1995; Schoeller et al., 1990), and it appears that obese individuals often do so to a greater extent than do normal-weight individuals (Heitmann and Lissner, 1995). Presently, a method for adjusting intakes to account for underreporting by individuals is not available and much work is needed to develop an acceptable method. Another important inherent inaccuracy is the quality of food composition databases and their applicability to what is or will actually be consumed when estimating intake or planning diets.

Furthermore, large day-to-day variations in intake, which are exhibited by almost all individuals, mean that it often takes a prohibitively large number of days of intake measurement to approximate usual intake (Basiotis et al., 1987; IOM, 2000). As a result, caution is indicated when interpreting nutrient assessments based on self-reported dietary data covering only a few days of intake. Data on nutrient intakes should be interpreted in combination with information on typical food usage patterns to determine if the recorded intakes are representative of an individual's usual intake.

Finally, because there is considerable variation in intakes both within and between individuals, as well as variation associated in estimating requirements, other factors must be evaluated in conjunction with the diet. The appropriate DRIs should be used in conjunction with other data in assessing the adequacy of the diet of a specific individual. The nutritional status of an individual can be definitively determined only by a combination of dietary, anthropometric, physiological, and biochemical data.

Using the Estimated Average Requirement and the Recommended Dietary Allowance for Assessment of Individuals

As is discussed in each chapter covering a specific nutrient, there were insufficient data to establish an Estimated Average Requirement (EAR) and therefore a Recommended Dietary Allowance (RDA) for the nutrients discussed in this report. Nevertheless, because these categories of DRIs exist for other nutrients, their use in the assessment of individuals will be described briefly.

The EAR is defined as estimating the median of the distribution of requirements for a specific life stage and gender group, but it is not possible to know where an individual's requirement falls within this distribution without further anthropometric, physiological, or biochemical measures. Thus from dietary data alone, it is only possible to estimate the *likelihood* of nutrient adequacy or inadequacy. The EAR is an amount that would meet the needs as defined for a chosen criterion of adequacy for half the individuals in the group to which the EAR is applied. The RDA is the amount that would meet the needs of almost all members of the group.

For practical purposes, many users of the DRIs may find it useful to consider that when observed intakes are below the EAR, they very likely need to be improved (because the probability of adequacy is 50 percent or less), and those between the EAR and the RDA probably need to be improved (because the probability of adequacy is less than 97 to 98 percent). Only if intakes have been

observed for a large number of days and are at the RDA, or observed intakes for fewer days are well above the RDA, should one have a high level of confidence that the intake is adequate. Such considerations are not applicable in the case of energy intake, which should match energy expenditure in individuals maintaining desirable body weight.

Using the Adequate Intake for Assessment of Individuals

Adequate Intakes (AIs) have been set for all nutrients discussed in this report for all life stage and gender groups, with the exception of sulfate. Equations that can be used to estimate the degree of confidence that an individual's usual intake meets or exceeds the AI have been developed (IOM, 2000). Usual individual intakes that are equal to or above the AI can be assumed to be adequate. However, the likelihood of inadequacy of usual intakes below the AI cannot be determined. For example, an adult with a usual potassium intake of 5 g/day could be assessed as having an adequate intake since intake exceeds the AI of 4.7 g/day. However, no conclusions regarding the adequacy of an intake of 3.5 g/day (i.e., below the AI) can be made since, by definition, when an AI is set there is insufficient information about the distribution of requirements. Accordingly, whether an intake below the AI meets an individual's requirement cannot be assessed since the requirement distribution is not known.

Using the Tolerable Upper Intake Level for Assessment of Individuals

The Tolerable Upper Intake Level (UL) is used to examine the possibility of over-consumption of a nutrient. Equations have been developed to determine the degree of confidence that an individual's estimated intake is actually below the UL (IOM, 2000). If an individual's usual nutrient intake remains below the UL, there is little risk of the identified adverse effect occurring from excessive intake. At chronic intakes above the UL, the potential for risk of adverse effects increases. However, the intake at which a given individual will develop the adverse effects associated with taking large amounts of one or more nutrients is not known with certainty. In this report, a UL has been established only for sodium. However, there is no established benefit to almost all healthy individuals who chronically consume amounts of nutrients that exceed the AI; it should be noted that acute adverse effects, which should be avoided,

do occur with excessive intakes of potassium, sulfate, and water, as discussed in the nutrient chapter.

ASSESSING NUTRIENT INTAKES OF GROUPS

The assessment of nutrient adequacy for groups of people requires unbiased, quantitative information on the intake of the nutrient of interest by individuals in the group. Care must be taken to ensure the quality of the information upon which assessments are made so that they are not underestimates or overestimates of nutrient intake. Estimates of total nutrient intake, including amounts from supplements, should be obtained. It is also important to use appropriate food composition tables with accurate nutrient values for the foods as consumed.

To assess the intake of a group, several steps must be taken. First, the intake distribution must be adjusted to remove the effect of day-to-day variation of individual intake. The statistical adjustments are based on assumptions about the day-to-day variation derived from repeat measurements of a representative subset of the group under study (Nusser et al., 1996). The resulting adjusted intake distribution narrows, giving a more precise estimate of the proportion of the group with usual intakes below the estimated requirements (Figure 8-2). An explanation of this adjustment procedure has been presented in previous reports (IOM, 2000, 2003).

For nutrients with an EAR, the prevalence of inadequacy in the population group for the nutrient evaluated is approximately the percent of the population evaluated whose intakes fall below the EAR, provided certain critical assumptions are met (IOM, 2000). Thus it is preferable to be able to establish an EAR where requirement data are available. However, for the nutrients in this report, inadequate or insufficient data on requirements of these nutrients for the indicators of adequacy prohibited establishing EARs.

Using the Adequate Intake in Group Assessment

In this report, Adequate Intakes (AIs) are assigned for total water, potassium, and sodium for all life stage and gender groups. Groups with median intakes equal to or above the AI for total water, potassium, and sodium can be assumed to have a low prevalence of inadequacy as determined by the criteria used to evaluate adequacy (provided that intake variability does not exceed that of the healthy group used to establish the AI). This would be particularly true for water, as the AI was set as a median intake of a presumably healthy

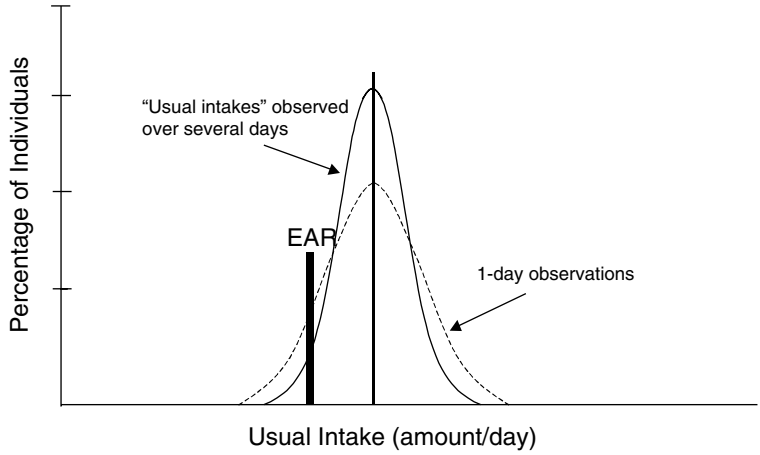

FIGURE 8-2 Comparison of 1-day and usual intakes for estimating the proportion of a group consuming below the Estimated Average Requirement (EAR).

group that demonstrated little evidence of dehydration. However, the AIs for sodium and potassium were not based on the median intakes of apparently healthy groups as there is a significant proportion of the population in the United States and Canada with hypertension and cardiovascular disease. Their AIs were based on experimental observations of intakes in small groups of people (frequently subjects in experimental trials) that appeared to meet the needs for a defined indicator of adequacy or functional outcome, such as lowered blood pressure. Thus, confidence in the assessment that the prevalence of inadequacy is low when median intake exceeds the AI will be less than it would be if the AIs represented the median intake of a healthy group (IOM, 2000).

Group median intakes below the AI, however, cannot be assumed to be inadequate. The reason for this is the same as discussed earlier for individuals, namely that when the distribution of requirements for the chosen criterion is not known, the adequacy of an intake below a "recommended level" cannot be determined. For example, although median intakes of potassium are considerably below the AI, no statements regarding the adequacy of potassium intakes of individuals in Canada and the United States can be made.

One can only point to the percent of individuals at or above the AI as indisputably having an adequate intake.

Using the Tolerable Upper Intake Level in Group Assessment

The proportion of the population with usual intakes below the Tolerable Upper Intake Level (UL) is likely to be at no risk of adverse effects due to overconsumption, assuming the data used to establish the UL accurately estimate the intake level at which a threshold for the adverse effect occurs. In the case where a threshold is not apparent, such as with sodium, lack of data may mean that a proportion of the population consuming intakes below the UL may potentially be at some risk. Thus, for sodium, for which the UL is 2.3 g/day, approximately 95 percent of men and 75 to 90 percent of women in the United States and Canada have sodium intakes above the UL (and probably even greater percentages will be above the UL given that salt added to foods at the table is not included in the estimated intake data), and could be considered to be at potential risk of increased blood pressure (the adverse effect used to set the UL for sodium). This coincides with that put the probability of becoming hypertensive at some point in the future at over 90 percent for individuals 55 years of age (Vasan et al., 2002).

The mean intake of a population cannot be used to evaluate the prevalence of intakes above the UL. A distribution of usual intakes, including intakes from supplements, is required to assess the proportion of the population that might be at risk of overconsumption. However, if the mean or median intake is equal to or greater than the UL, as is the case for sodium, it suggests that the number of individuals with excessive intake is high and warrants further investigation.

PLANNING NUTRIENT INTAKES OF INDIVIDUALS

Using the Adequate Intake in Planning for Individuals

Adequate Intakes (AIs) are set for all nutrients in this report but sulfate. The AI for term infants is based on human milk, which provides adequate amounts in the case of most nutrients, so it is not necessary to plan additional sources of intakes for infants exclusively fed human milk. Likewise, an infant formula with a nutrient profile similar to human milk (after adjustment for differences in bioavailability) should supply adequate nutrients for an infant. Other age groups (children, adolescents, and adults) should use

the AI as their goal for intake of water, potassium, and sodium chloride. Guidance for using AIs for labeling was recently developed (IOM, 2003).

Using the Tolerable Upper Intake Level in Planning for Individuals

In this report, a Tolerable Upper Intake Level (UL) was set only for sodium. Thus individuals should plan their intakes to remain below the UL for sodium. Guidance for how to incorporate ULs when establishing dietary values for nutrition labels was recently proposed (IOM, 2003).

PLANNING NUTRIENT INTAKES OF GROUPS

Using the Adequate Intake in Planning for Groups

Planning a group median intake that meets the Adequate Intake (AI) should, by definition, be associated with a low prevalence of inadequacy when the AI is set as the median intake of a healthy group and the group being planned for has characteristics similar to the group used to establish the AI (IOM, 2000). If the AI is not set as the median intake of a healthy group (e.g., the AIs for sodium and potassium were not set in this way), one would have less confidence that the prevalence of inadequacy would be low if the group's median intake met the AI.

Using the Tolerable Upper Intake Level in Planning for Groups

In order to minimize the proportion of the population at potential risk of adverse effects from excessive nutrient intake, the distribution of usual intakes should be planned so that the prevalence of intakes above the Tolerable Upper Intake Level (UL) is acceptably low (IOM, 2003). Since a large majority of the population has usual intakes of sodium above the UL, this will necessitate a dramatic reduction in population sodium intakes.

NUTRIENT-SPECIFIC CONSIDERATIONS

Water

The Adequate Intake (AI) for *total* (drinking water, beverages, and food) water set in this report is derived from the median total water intakes from U.S. dietary survey data expressed as absolute amounts (liters/day), and varies by age and gender. For example,

the AI for men 19 to 30 years of age is set at 3.7 L/day of *total* water (from foods and fluids), while for women in the same age group, the AI is set at 2.7 L/day. In dietary survey data (Appendix Tables D-3 and F-1), water from food provided 19 percent of *total* water intake, or 0.7 L/day for men and 0.5 L/day for women in the United States (Appendix Table D-4). Fluids (drinking water and beverages) consumed were 3.0 L (about 12 cups)/day and 2.2 L (9¼ cups)/day for 19- to 30-year-old men and women, respectively, which represented about 81 percent of *total* water intake (Appendix Table D-3). Individuals who meet the recommended 60 minutes per day of moderate physical activity (IOM, 2002/2005) can easily meet the AI for *total* water through drinking water, beverages, and food (see Table 4-15).

A number of foods (especially fruits and vegetables) contain a substantial amount of water (moisture) (see Table 4-14). Unlike most other nutrients, intake of water is driven by need, as well as other factors. Because excessive water consumption does not occur in healthy people, no Tolerable Upper Intake Level (UL) was set. It is possible to meet the AI for *total* water by consuming little or no plain water, but instead by consuming a mixed diet (including fruits and vegetables, most of which are over 90 percent water by weight; meat, fish, and poultry, which contain about 60 to 70 percent water by weight; and other beverages, such as fruit juices and milk [see Table 4-14]).

As discussed in Chapter 4, it is important to note that water requirements cannot be considered in isolation from macronutrient and electrolyte consumption because these nutrients are critical to water balance. In addition, an individual's water requirement can vary extensively due to physical activity levels and exposure to varied environments. The majority of body water is associated with fat-free mass (70 to 75 percent) in adults. Total body water averages approximately 60 percent of body weight with a range of 45 to 75 percent due primarily to differences in body composition. Total body water deficits of as little as 2 percent of body weight (e.g., a loss of 1.4 kg [about 1.4 L] in a 70-kg adult) can significantly impair both cognitive function and motor control.

Diet composition, physical activity level, environmental exposure, pathophysiological factors (e.g., diabetes mellitus, cystic fibrosis, renal disease), and use of diuretics or other medications all impact water needs, which vary daily.

The increase in solute loads of various beverages (e.g., milk or sports drinks) are minimal in terms of need to adjust the volume to correct for additional excretory load. Ingestion of fluids containing

caffeine and alcohol, known to result in diuresis, are not associated with increased incidence of dehydration or body water deficits; thus their consumption can contribute to the total body water needs of individuals (IOM, 2001; Taivainen et al., 1995).

Potassium

As described in detail in Chapter 5, potassium is the major intracellular cation and is required for normal cellular function. An AI of 4.7 g (120 mmol)/day has been established for potassium for all adults. This level is based on an intake of naturally occurring potassium from dietary sources, primarily fruits and vegetables, which has been shown to be beneficial in reducing the adverse effects of sodium intake on blood pressure and possibly in reducing the risk of kidney stones. Bicarbonate or its precursors (organic anions typically associated with potassium in foods) may neutralize an excess acid load seen in typical Western-style diets, and may diminish bone turnover. Because potassium intakes from naturally occurring dietary sources above the AI have not been found to result in increased risk of adverse effects in generally healthy individuals with normal kidney function (excess potassium is readily excreted in the urine), no UL was set. Caution is warranted, however, in the consumption of potassium by individuals whose kidney function may be insufficient to excrete potassium adequately; in individuals taking medications known to decrease renal excretion of potassium (e.g., angiotensin converting enzyme [ACE] inhibitors and angiotensin II-blockers [ARBs]); and in individuals who have diseases known to alter potassium metabolism, such as diabetes.

In assessing and planning for potassium intakes of individuals, important considerations that impact potassium requirements include the effects of environmental heat exposure and physical activity levels on potassium loss through sweat and the use of diuretics or other drug therapies commonly prescribed for the treatment of hypertension and congestive heart failure. These factors have the potential to influence potassium needs because they increase potassium losses in urine and sweat.

In most cases, however, losses in sweat are unlikely to be extreme, and the AI should provide an appropriate amount of potassium. Individuals who use diuretics should follow advice from their physician regarding potassium intake and the need for supplements since the type of diuretic used can affect whether appreciable amounts of potassium are lost in the urine.

In contrast, there are some clinical situations in which potassium is retained and a high intake could pose a risk. These include individuals with chronic renal insufficiency, end-stage renal disease, severe heart failure, diabetes, adrenal insufficiency, and ACE inhibitor therapy. For these individuals, the AI may be too high a level to consume. Once again, medical advice should be obtained, and use of potassium-containing salt substitutes should be undertaken only when advised by a physician.

In planning diets for individuals and for groups, the dietary source of potassium is also important. Naturally occurring potassium is the cation found most abundantly in vegetable fruits (e.g., tomatoes, cucumbers, zucchini, eggplant), leafy greens, and roots (e.g., carrots, radishes, turnips, onions) and is present with bicarbonate, citrate, or other organic anions. In contrast, the potassium added to foods or found in supplements is primarily in the form of potassium chloride. Potassium bicarbonate administration produces lower levels of calcium in urine compared with potassium chloride, suggesting that potassium bicarbonate or citrate are the forms most conducive to a reduced risk of renal stones. Because bicarbonate, but not chloride, can neutralize the acid generated from the metabolism of diets high in animal proteins, resulting in less bone turnover, potassium chloride also would not be expected to promote bone health as would be predicted with potassium bicarbonate. Although neither of these potential health benefits (i.e., reduced risk of renal stones and bone loss) can be attributed to potassium *per se*, they occur as a consequence of consuming diets rich in natural sources of potassium.

While the U.S. population and, to a lesser extent, the Canadian population consume diets well below the AI of 4.7 g/day recommended for adults, increasing intake of good sources of potassium, such as fruits and vegetables, should enable individuals to meet the AI for potassium (see Table 5-8).

Sodium Chloride

Sodium is the principle cation of the extracellular fluids and is the primary regulator of extracellular fluid volume and body water. Sodium and chloride are normally consumed together as sodium chloride (salt) in food. For this reason, Chapter 6 presents data on recommended intakes and effects of sodium as sodium chloride and assumes it applies to chloride unless otherwise noted. However, for planning purposes, the AI is presented as grams per day of so-

dium rather than of sodium chloride. While the minimal amount of sodium required to replace insensible losses is estimated to be 0.18 g (7.8 mmol)/day under conditions of maximal adaptation and without sweating, the sodium AI has been set at 1.5 g/day. Sodium intake at this level would be adequate to cover losses from sweating among those who are moderately active, as recommended (IOM, 2002/2005), as well as to meet nutrient needs for other important nutrients using dietary patterns typical of the United States and Canada. Since median intakes of the U.S. population are well above the AI, the prevalence of inadequacy is likely to be extremely low.

Approximately 98 percent of sodium chloride consumed is absorbed over a wide range of intakes, and approximately 90 to 95 percent of sodium excretion occurs through the urine, with losses in sweat being minimal among those who do not experience sweat loss due to exercise. However, physical activity levels can have a substantial impact on sweat sodium losses; therefore, the AI of 1.5 g/day does not apply to individuals who lose large volumes of sodium in sweat, such as competitive athletes and workers exposed to extreme heat stress (e.g., foundry workers and fire fighters). For example, sweat losses during exercise in the heat may easily exceed 1 L/hour with a sodium concentration of greater than 35 to 50 mmol (0.8 to 1.15 g)/L. Thus it would be prudent for individuals who exercise strenuously on a daily basis to carefully monitor their electrolyte intake as well as their water intake.

As sodium chloride intake increases, several dose-dependent changes occur. Increased sodium chloride intake increases blood pressure, and it is associated with an increased risk of cardiovascular outcomes (particularly left ventricular hypertrophy and stroke), and possibly with an increased risk of asthma and gastric cancer. It also causes increased urinary excretion not only of sodium chloride, but also of calcium. For these reasons, a UL of 2.3 g (100 mmol)/day has been set for sodium. As described earlier, a large majority of the U.S. population has sodium intakes in excess of the UL. Reducing sodium intakes to levels below the UL will be challenging because of the ubiquitous presence of salt in processed foods. For example, although the menu in Table 6-10 is below the UL with about 1.6 g of sodium, this was attained only by minimizing the use of processed foods; by using unsalted margarine; by preparing vegetables and rice without the addition of salt to cooking water; and by avoiding the use of salt at the table.

Although the AI is not dependent on energy intake, from a practical viewpoint, the more individuals eat, the more sodium they consume, unless they purposely choose foods lower in sodium. For ex-

ample, in the DASH-sodium trial, sodium intakes were adjusted by energy level. At the lowest level of sodium intake, individuals consuming 1,600 kcal received 0.90 g (40 mmol)/day of sodium; at 2,100 kcal, 1.15 g (50 mmol)/day of sodium; at 2,600 kcal, 1.38 g (60 mmol)/day; at 3,100 kcal, 1.60 g (70 mmol)/day of sodium; and at 3,600 kcal/day, 1.8 g (80 mmol)/day of sodium (Svetkey et al., 1999).

The median range of estimated energy intakes for men and women 19 to 50 years of age in the latest Continuing Survey of Food Intake by Individuals (CSFII) (1994–1996, 1998) was ≈ 2,476 to 2,718 kcal/day and 1,659 to 1,757 kcal/day, respectively (IOM, 2002/2005), or an average overall median energy intake of 2,150 kcal/day. An active lifestyle has been recommended that requires approximately 3,100 and 2,400 kcal/day for young men and women, respectively (IOM, 2002/2005). Those individuals who are more physically active and therefore require more energy than median intakes observed in the CSFII data (IOM, 2002/2005) will likely consume sodium in excess of the AI. In contrast, those individuals who consume a lower intake of energy (e.g., 1,600 kcal/day) and who are physically inactive would likely have an adequate sodium intake with intakes below the AI. Of course, with restricted energy intake, careful dietary planning would be needed to meet recommended intakes for other nutrients.

Sodium chloride needs may be affected in a number of clinical conditions. For example, use of diuretics has been reported to lead to hyponatremia, although this appears to be a consequence of impaired water excretion rather than of excessive sodium loss since it can be corrected by water restriction. Other clinical states that can lead to increased renal salt losses include adrenal cortical insufficiency, intrinsic renal disorders (e.g., oliguric renal failure, medullary cystic disease, nephrocalcinosis), and certain diseases (e.g., cystic fibrosis, diabetes). In these situations, sodium should not be unduly restricted, and medical advice appropriate for the individual should be obtained.

SUMMARY

Dietary Reference Intakes (DRIs) may be used to assess nutrient intakes as well as for planning nutrient intakes. Box 8-1 summarizes the appropriate uses of the DRIs for individuals and groups.

BOX 8-1 Uses of Dietary Reference Intakes for Healthy Individuals and Groups

Type of Use	*For an Individual*[a]	*For a Group*[b]
Assessment	**EAR:** use to examine the probability that usual intake is inadequate (if individual's usual intake is at the EAR, then 50% probability that intake is inadequate).	**EAR:** use to estimate the prevalence of inadequate intakes within a group (% in a group whose intakes are inadequate = % whose intakes are below the EAR).
	RDA: usual intake at or above this level has a low probability of inadequacy.	**RDA:** do not use to assess intakes of groups.
	AI[c]**:** usual intake at or above this level has a low probability of inadequacy.	**AI**[c]**:** mean usual intake at or above this level implies a low prevalence of inadequate intakes.
	UL: usual intake above this level may place an individual at risk of adverse effects from excessive nutrient intake.	**UL:** use to estimate the percentage of the population at potential risk of adverse effects from excess nutrient intake.

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Type of Use	*For an Individual*[a]	*For a Group*[b]
Planning	**RDA:** aim for this intake.	**EAR:** use to plan an intake distribution with a low prevalence of inadequate intakes.
	AI[c]**:** aim for this intake.	**AI**[c]**:** use to plan mean intakes.
	UL: use as a guide to limit intake; chronic intake of higher amounts may increase the potential risk of adverse effects.	**UL:** use to plan intake distributions with a low prevalence of intakes potentially at risk of adverse effects.

RDA = Recommended Dietary Allowance
EAR = Estimated Average Requirement
AI = Adequate Intake
UL = Tolerable Upper Intake Level

[a] Evaluation of true status requires clinical, biochemical, and anthropometric data.
[b] Requires statistically valid approximation of distribution of usual intakes.
[c] For the nutrients in this report, AIs are set for all age groups for water, potassium, and sodium (and chloride on an equimolar basis to sodium). The AI may be used as a guide for infants as it reflects the average intake from human milk. Infants consuming formulas with the same nutrient composition as human milk are consuming an adequate amount after adjustments are made for differences in bioavailability. In the context of assessing groups, when the AI for a nutrient is not based on mean intakes of a healthy population, this assessment is made with less confidence. The use of other DRIs (the Estimated Energy Requirement [EER] and the Acceptable Macronutrient Distribution Range [AMDR]) are described in another report in this series (IOM, 2002/2005).

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9
A Research Agenda

The Panel on Electrolytes and Water under the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes was charged with developing a research agenda to provide a basis for public-policy decisions related to recommended intakes of water, potassium, sodium, chloride, and sulfate. This chapter describes the approach used to develop the research agenda, briefly summarizes gaps in knowledge, and presents a list of research topics deemed of highest priority. Sections at the end of Chapters 4 through 7 present additional research topics.

APPROACH

During its deliberations, the panel critically reviewed the published literature on the health effects of water, potassium, sodium, chloride, and sulfate. Throughout the process of preparing this report, the panel:

1. Identified gaps in knowledge related to role of electrolytes and water in human health and their impact on functional and biochemical indicators used to assess requirements; methodological problems in measuring electrolyte and water intake and in assessing adequacy of intake; relationships of nutrient intake to chronic disease; and adverse effects from overconsumption of electrolytes and water.
2. Examined data to identify major discrepancies between intake

and the recommended intakes and consider possible reasons for such discrepancies.

3. Considered the need to protect individuals with extreme or distinct vulnerabilities due to disease conditions or genetic predisposition.

4. Weighed the alternatives and set priorities based on expert judgment.

MAJOR KNOWLEDGE GAPS

Requirements

To derive an Estimated Average Requirement (EAR), a criterion must be selected for a particular status indicator or combination of indicators that is consistent with impaired status as defined by some clinical consequence or accepted biomarker for that consequence.

- For sodium, potential biochemical indicators of adequate intake included increased plasma renin activity, adverse changes in lipid concentrations, and increased insulin resistance. Nonbiochemical indicators were nutrient inadequacy and sodium imbalance. In predominantly short-term studies, a reduced sodium intake increased plasma renin activity, but the clinical relevance of increased plasma renin activity is uncertain. The best available evidence did not support adverse changes to lipid concentrations. Data were insufficient to determine whether chronic ingestion of sodium in clinically relevant ranges led to deterioration in insulin resistance. Achieving an adequate intake of other nutrients is a potential concern at extremely low levels of intake. Sodium imbalance, that is, sodium losses that exceed intake, might occur when sweat sodium losses are high, as in the setting of extreme heat or extreme physical activity, particularly in persons who are unacclimatized to these environmental conditions. Overall, there was no single indicator that could be used to assess adequacy of intake, and thus a combination of indicators was used.
- For potassium, serum potassium concentration and hypokalemia are insensitive markers of inadequate intake. Biochemical markers of inadequate potassium intake are needed.
- For water, plasma or serum osmolality is an acceptable indicator of hydration status; however, trials that rigorously control and test different levels of total water intake, rather than allowing *ad libitum* intakes, have not been performed.

- For sulfate, there is no identified indicator of inadequate intake. Requirements for sulfate are met by meeting dietary protein and sulfur amino acid recommendations.
- For water, potassium, and sodium, useful data are lacking for setting requirements for infants, children, adolescents, pregnant and lactating women, and the elderly. As an example, there is a paucity of data on the relationship of dietary sodium and potassium intakes early in life on blood pressure and markers of bone health during adulthood. For water, research studies commonly tested the effects of inadequate intake in men of military age, but not in broad populations.

Methodology

In free-living persons, accurate measurement of dietary water and electrolytes intake is difficult, as are measurements of total body water and electrolytes. Potential sources of error in self-reported intake data include underreporting of portion sizes and frequency of intake, omission of foods and beverages, and use of food composition tables, which need to be continuously updated and expanded to include new foods and reformulated products.

For several reasons, assessment of sodium intake is problematic. Substantial additions can occur after processing. In fact, many diet collection methods do not collect information on the salt (sodium chloride) added during cooking or eating. More importantly, there is large day-to-day variation in sodium intake. The most accurate method to assess dietary sodium is to measure several timed urinary collections. However, this approach is cumbersome and prone to collection errors. Hence, practical tools to estimate sodium intake are needed.

Relationships of Intake to Chronic Disease

A substantial body of evidence, including results of clinical trials, has documented that reduced dietary sodium intake and increased potassium intake can lower blood pressure, which itself is a powerful risk factor for cardiovascular disease. Several, but not all, observational studies link increased dietary sodium and reduced potassium intake with subsequent cardiovascular disease. There is also evidence that increased dietary sodium intake and inadequate potassium intake increase urinary calcium excretion and affect calcium balance, but evidence of their effects on subclinical and clini-

cal outcomes, such as bone mineral density and osteoporosis, is limited.

Ideally, trials that test the effects of sodium reduction and increased potassium intake, alone and combined, on clinical outcomes should be conducted, potentially with multiple levels of intake. However, a critical issue is the feasibility of such efforts, an issue that pertains not just to sodium and potassium, but also to other nutrients (e.g., *trans* fatty acids and cholesterol) and nondietary factors (e.g., exercise and smoking) associated with the development of chronic disease. Feasibility concerns include the difficulties in sustaining a sufficient experimental contrast, large sample size, extended follow-up periods, and high cost. For these reasons, a trial that tests the effects of sodium reduction on clinical cardiovascular outcomes in hypertensive individuals, much less nonhypertensive individuals, is probably not possible. Still, debate on the overall health effects of sodium persists. Hence, a formal assessment of the feasibility of a trial of sodium reduction on clinical cardiovascular outcomes should be undertaken, and the results of this assessment should be published. For other research issues, such as the effects of increased potassium intake on stroke, kidney stones, or bone mineral density, clinical trials are more feasible. If possible, dose-response trials should be conducted.

For sulfate, a high priority is determining whether an increased sulfate intake increases the risk of inflammatory bowel disease. This research issue might be addressed in the setting of a case-control study or possibly a large, prospective observational study.

For water, there is a paucity of evidence on the effects of habitually low intakes on chronic disease outcomes (e.g., kidney stones, bladder cancer, and urinary tract infections). The effects of increased water intake as a means to prevent recurrent kidney stones and urinary tract infections could be tested in clinical trials, while the relationship between water intake and bladder cancer could be addressed in observational studies.

THE RESEARCH AGENDA

Three major types of information gaps were noted: (1) a paucity of data for estimating average requirements for electrolytes and water in presumably healthy humans; (2) an even greater dearth of evidence on the electrolyte and water needs in infants, children, adolescents, the elderly, and pregnant women; and (3) a lack of multidose trials to determine the effects of electrolyte and water intake on chronic diseases. There is also a critical need for research

on public health strategies that effectively reduce sodium intake and others that increase potassium intake in the general population.

Highest priority is given to research that has the potential to prevent or retard human disease processes and to prevent deficiencies with functional consequences. The following broad areas for research were deemed the highest priority (specific research recommendations are found at the conclusions of Chapters 4 through 7):

- Research on effective public health strategies to achieve and sustain a reduced sodium and increased potassium intake in the general population, including
  - behavioral change studies in individuals, and
  - community-based intervention studies.
- Research on alternative technologies that reduce the sodium content of foods, with a special emphasis on maintaining flavor, texture, consumer acceptability, safety, and low cost.
- Studies that test the effects of reduced sodium and increased potassium intake, alone and combined, on clinical outcomes (e.g., stroke, bone mineral density, and kidney stones). To the extent possible, clinical trials should be conducted. A formal assessment of the feasibility of a sodium reduction trial with clinical cardiovascular outcomes should be undertaken. In the absence of trials, methodologically rigorous observational studies that concomitantly collect electrolyte intake, other dietary information, and genetic information should be conducted.
- Studies to assess the potential for increased potassium intake to mitigate the adverse consequences of excess sodium intake and, vice versa, the potential for a reduced sodium intake to mitigate the adverse consequences of inadequate potassium intake. Potential outcomes include blood pressure, salt sensitivity, bone demineralization, and bone mineral density.
- Studies on the adverse effects of chronic, low-grade metabolic acidosis that results from an inadequate intake of potassium and its bicarbonate precursors. Potential outcomes include bone mineral density and kidney stones.
- Water, sodium, and potassium balance studies that enroll broad populations and that vary climate and physical activity levels. Populations of particular interest are children, as well as older persons with chronic, but stable, illnesses.
- Research to improve the assessment of sodium and potassium intake and total body stores.

- Studies to determine whether increased water intake can prevent kidney stones and urinary tract infections.
- Studies that assess the effects of sodium and potassium intake during childhood on the development of chronic diseases during adulthood.
- Studies to assess the relationship between sulfate intake and inflammatory bowel disease.

A
Glossary and Acronyms

ACE	Angiotensin converting enzyme
Adverse effect	Any significant alteration in the structure or function of the human organism, or any impairment of a physiologically important function, that could lead to an adverse health effect
AI	Adequate Intake; a category of Dietary Reference Intakes; an amount of a nutrient that is a recommended intake for a life stage or gender group for which it is established and is based on experimentally derived intake levels or approximations of observed mean nutrient intakes by a group (or groups) of healthy people
ANP	Atrial natriuretic peptide
ARB	Angiotensin II receptor blocker
BIA	Bioelectric impedance analysis
CDC	Centers for Disease Control and Prevention; an agency of the U.S. Department of Health and Human Services
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane regulatory gene
CHD	Coronary heart disease
CID	Cold-induced diuresis
CSFII	Continuing Survey of Food Intakes by Individuals; a survey conducted periodically by the Agri-

	cultural Research Service, U.S. Department of Agriculture
CVD	Cardiovascular disease; includes heart disease and stroke
DASH Diet	Dietary Approaches to Stop Hypertension; a diet rich in fruits, vegetables, and low-fat dairy products and reduced in saturated fat, total fat, and cholesterol
DASH-Sodium Trial	A clinical trial that tested the effects on blood pressure of three different sodium levels in two distinct diets
DASH Trial	A clinical trial that tested the effects of different dietary patterns on blood pressure
Dehydration	The process of decreasing total body water; lower than normal total body water (euhydration) (see hypohydration)
DEXA	Dual energy X-ray absorptiometry
Dose-response assessment	Second step in a risk assessment in which the relationship between nutrient intake and an adverse effect (in terms of incidence or severity of the effect) is determined
DRI	Dietary Reference Intakes
EAR	Estimated Average Requirement; a category of Dietary Reference Intakes; an amount of a nutrient that is estimated to meet the requirement, as defined by the specified indicator or criterion of adequacy, of half of the apparently healthy individuals in the life stage or gender group for which it is established
ECF	Extracellular fluid
ECG	Electrocardiogram
EPA	U.S. Environmental Protection Agency
Euhydration	Normal hydration
FDA	Food and Drug Administration; an agency of the U.S. Department of Health and Human Services
FFM	Fat-free mass
FNB	Food and Nutrition Board; a division of the Institute of Medicine of the National Academies

Function	Role played by a nutrient in growth, development, and maturation
GFR	Glomerular filtration rate
Hazard identification	First step in a risk assessment, which is concerned with the collection, organization, and evaluation of all information pertaining to the toxic properties of a nutrient
Health Canada	The federal department in Canada responsible for maintaining and improving the health of Canadian people
HDL	High-density lipoprotein
Hyperhydration	Higher than normal total body water (euhydration)
Hyperkalemia	Serum potassium concentration > 5.0 mEq/L or mmol/L
Hypernatremia	Serum sodium concentration > 145 mEq/L or mmol/L
Hypertension	Systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 mm Hg
Hypohydration	Lower than normal total body water (euhydration) (see dehydration)
Hypokalemia	Serum potassium concentration < 3.5 mEq/L or mmol/L
Hyponatremia	Serum sodium concentration < 135 mEq/L or mmol/L
ICF	Intracellular fluid
IOM	Institute of Medicine
LDL	Low-density lipoprotein
LOAEL	Lowest-observed-adverse-effect level; the lowest intake (or experimental dose) of a nutrient at which an adverse effect has been identified
MAP	Mean arterial pressure; diastolic pressure times 2 plus systolic pressure over 3; the average pressure during a cardiac cycle
MCL	Maximum contaminant level; a level set by the U.S. Environmental Protection Agency for environmental contaminants

MVP	Mitrial valve prolapse
NFCS	Nationwide Food Consumption Survey; a food consumption survey conducted through 1965 by the U.S. Department of Agriculture
NHANES	National Health and Nutrition Examination Survey; a survey conducted periodically by the National Center for Health Statistics, Centers for Disease Control and Prevention
NOAEL	No-observed-adverse-effect level; the highest intake (or experimental dose) of a nutrient at which no adverse effect has been observed
NRC	National Research Council
PAPS	3′-phosphoadenosine-5′-phosphosulfate
Psychogenic polydipsia	The excessive consumption of fluid, especially water, among chronic psychiatric patients, particularly those with schizophrenia
RDA	Recommended Dietary Allowance; a category of Dietary Reference Intakes; an amount of a nutrient that is the recommended average daily dietary intake level that is sufficient to meet the requirement of nearly all (97 to 98 percent) healthy individuals in the particular life stage and gender group for which it is established; it is derived from the Estimated Average Requirement
Rhabdomyolysis	Injury to skeletal muscle tissue that results in the destruction of skeletal muscle cells and allows for the escape of cellular contents into the extracellular fluid, leading to renal failure and compartment syndromes
Risk assessment	The organized framework for evaluating scientific information that has as its objective a characterization of the nature and likelihood of harm resulting from excess human exposure to an environmental agent (in this case, a nutrient); it includes the development of both qualitative and quantitative expressions of risk
Risk characterization	The final step in a risk assessment, which summarizes the conclusions from steps 1 through 3 of the assessment (hazard identification, dose

	response, and estimate of exposure) and evaluates the risk; this step also includes a characterization of the degree of scientific confidence that can be placed in the Tolerable Upper Intake Level
Risk management	Process by which risk assessment results are integrated with other information to make decisions about the need for, method of, and extent of risk reduction; in addition, it considers such issues as the public health significance of the risk, the technical feasibility of achieving various degrees of risk control, and the economic and social costs of this control
Salt sensitivity	The extent of blood pressure change in response to a reduction in salt intake; the term "salt-sensitive blood pressure" applies to those individuals or subgroups who experience the greatest reduction in blood pressure from a given reduction in salt intake
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SHRSP	Stroke-prone spontaneously hypertensive (inbred strain of rats)
TBW	Total body water
TOHPII	Trials of Hypertension Prevention-Phase II: a clinical trial that tested the effects of sodium reduction and weight loss, alone or combined, as a means to prevent hypertension
Total water	Includes drinking water, water in beverages, and water that is part of food
UF	Uncertainty factor; the number by which the NOAEL (or LOAEL) is divided to obtain the Tolerable Upper Intake Level; the size of the UF varies depending on the confidence in the data and the nature of the adverse effect
UL	Tolerable Upper Intake Level; a category of Dietary Reference Intakes; the amount of a nutrient that is the highest level of daily intake likely to pose no risk of adverse health effects for al-

	most all apparently healthy individuals in the specified life stage group for which it is established
USDA	U.S. Department of Agriculture
WBGT	Wet bulb globe temperature
WHO	World Health Organization

B

Origin and Framework of the Development of Dietary Reference Intakes

This report is the sixth in a series of publications resulting from the comprehensive effort being undertaken by the Food and Nutrition Board's (FNB) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (DRI Committee) and its panels and subcommittees.

ORIGIN

This initiative began in June 1993, when FNB organized a symposium and public hearing entitled, "Should the Recommended Dietary Allowances Be Revised?" Shortly thereafter, to continue its collaboration with the larger nutrition community on the future of the Recommended Dietary Allowances (RDAs), FNB took two major steps: (1) it prepared, published, and disseminated the concept paper, "How Should the Recommended Dietary Allowances Be Revised?" (IOM, 1994), which invited comments regarding the proposed concept, and (2) it held several symposia at nutrition-focused professional meetings to discuss FNB's tentative plans and to receive responses to the initial concept paper. Many aspects of the conceptual framework of the DRIs came from the United Kingdom's report, *Dietary Reference Values for Food Energy and Nutrients for the United Kingdom* (COMA, 1991).

The five general conclusions presented in FNB's 1994 concept paper were:

1. Sufficient new information has accumulated to support a reassessment of the RDAs.
2. Where sufficient data for efficacy and safety exist, reduction in the risk of chronic degenerative disease is a concept that should be included in the formulation of future recommendations.
3. Upper levels of intake should be established where data exist regarding risk of toxicity.
4. Components of food of possible benefit to health, although not meeting the traditional concept of a nutrient, should be reviewed, and if adequate data exist, reference intakes should be established for these components.
5. Serious consideration must be given to developing a new format for presenting future recommendations.

Subsequent to the symposium and the release of the concept paper, FNB held workshops at which invited experts discussed many issues related to the development of nutrient-based reference values, and FNB members have continued to provide updates and engage in discussions at professional meetings. In addition, FNB gave attention to the international uses of the earlier RDAs and the expectation that the scientific review of nutrient requirements should be similar for comparable populations.

Concurrently, Health Canada and Canadian scientists were reviewing the need for revision of the *Recommended Nutrient Intakes* (RNIs) (Health Canada, 1990). Consensus following a symposium for Canadian scientists, cosponsored by the Canadian National Institute of Nutrition and Health Canada in April 1995, was that the Canadian government should pursue the extent to which involvement with the developing FNB process would benefit both Canada and the United States in leading toward harmonization.

Based on extensive input and deliberations, FNB initiated action to provide a framework for the development and possible international harmonization of nutrient-based recommendations that would serve, where warranted, for all of North America. To this end, in December 1995, FNB began a close collaboration with the government of Canada and took action to establish the DRI Committee.

THE CHARGE TO THE COMMITTEE

In 1995, the DRI Committee was appointed to oversee and conduct this project. To accomplish this task over a decade, the DRI Committee devised a plan involving the work of seven or more ex-

pert nutrient group panels and two overarching subcommittees (Figure B-1). The process described below for this report is expected to be used for subsequent reports.

The Panel on DRIs for Electrolytes and Water, composed of experts on these nutrients, was asked to (1) review the scientific literature regarding water and dietary potassium, sodium, chloride, and sulfate to determine the roles, if any, they play in health; (2) review selected components of food that may influence the bioavailability of these compounds, as well as their interaction with each other; (3) develop estimates of dietary intake of these compounds that are compatible with good nutrition throughout the lifespan and that may decrease risk of chronic disease where data indicate they play a role; (4) determine Tolerable Upper Intake Levels (ULs) for each compound where scientific data are available in specific population subgroups; and (5) identify research needed to improve the knowledge of the role of electrolytes and water in health.

The panel was charged with analyzing the literature, evaluating possible criteria or indicators of adequacy, and providing substantive rationales for their choices of each criterion. Using the crite-

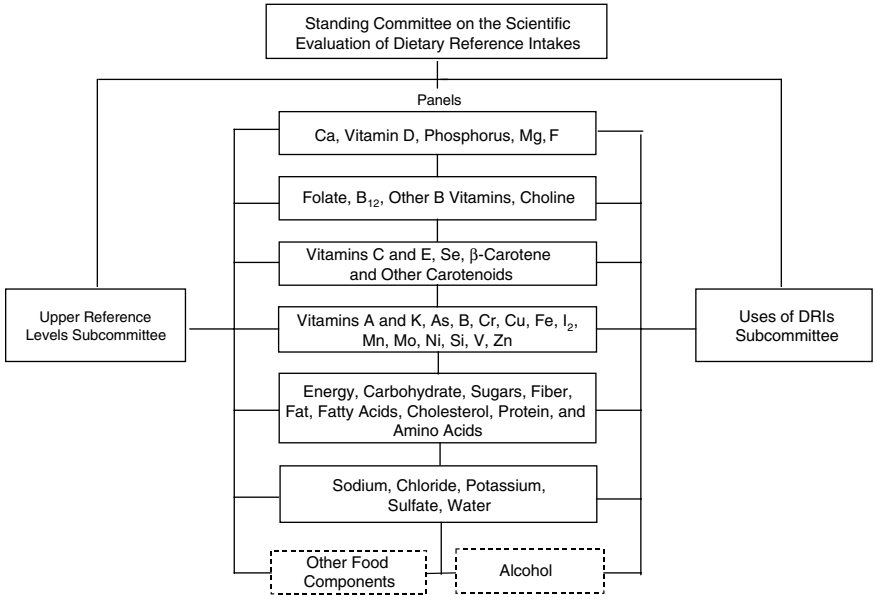

FIGURE B-1 Dietary Reference Intakes project structure.

rion chosen for each stage of the lifespan, the panel estimated the average requirement for each nutrient or food component reviewed, assuming that adequate data were available. As the panel members reviewed data on ULs, they also interacted with the Subcommittee on Upper Reference Levels of Nutrients (UL Subcommittee), which assisted the panel in applying the risk assessment model to each selected nutrient. The DRI values in this report are a product of the joint efforts of the panel and the DRI Committee.

ISSUES OF RELEVANCE FROM PAST DIETARY REFERENCE INTAKE REPORTS

Methodology to Develop Estimated Average Requirements and Recommended Dietary Allowances When Requirements for Nutrients Are Not Normally Distributed

For most of the nutrients for which Estimated Average Requirements (EARs) have been established, the required assumption of distribution of requirements among the groups for which the EAR was developed is that of symmetry about the mean. In the case of iron, a nutrient of concern in many subgroups in the population in the United States, Canada, and other areas, requirements are known to follow a non-normal distribution. Thus a different method was needed to determine the intake of iron at which half of the individuals would be expected to be inadequate in the criterion used to establish adequacy (the EAR), and also to construct an intake level at which only a small percentage of the population would be inadequate (the RDA).

If the requirement of a nutrient is not normally distributed but can be transformed to normality, its EAR and RDA can be estimated by transforming the data, calculating the 50th and 97.5th percentiles, and transforming these percentiles back into the original units. In this case, the difference between the EAR and the RDA cannot be used to obtain an estimate of the standard deviation of the coefficient of variation because skewing is usually present.

Where factorial modeling is used to estimate the distribution of requirement from the distributions of the individual components of requirement, as was done in the case of the iron recommendations (IOM, 2001), it is necessary to add the individual distributions (convolutions). This is easy to do given that the average requirement is simply the sum of the averages of the individual component distributions, and a standard deviation of the combined distribution can be estimated by standard statistical techniques. The 97.5th

percentile can then be estimated (for a further elaboration of this method, see Chapter 9 and Appendix I of *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* [IOM, 2001]).

If normality cannot be assumed for all of the components of requirement, then Monte Carlo simulation is used for the summation of the components. This approach models the distributions of the individual distributions and randomly assigns values to a large simulated population. The total requirement is then calculated for each individual and the median and the 97.5th percentile are calculated directly. As was the case for iron (IOM, 2001), the underlying joint distribution is approximated and a large number of individuals (100,000) is randomly generated. Information about the distribution of values for the requirement components is modeled on the basis of known physiology. Monte Carlo approaches may be used in the simulation of the distribution of components, or where large data sets exist for similar populations (e.g., growth rates in infants), estimates of relative variability may be transferred to the component in the simulated population (Gentle, 1998). At each step, the goal is to achieve distribution values for the component that not only reflect known physiology or known direct observations, but that can also be transformed into a distribution that can be modeled and used in selecting random members to contribute to the final requirement distribution. When the final distribution representing the convolution of components has been derived, then the median and 97.5th percentile of the distribution can be directly estimated. It is recognized that in its simplest form, the Monte Carlo approach ignores possible correlation among components. In the case of iron, however, expected correlation is built into the modeling of requirement where components are linked to a common variable, such as growth rate, so that not all sources of correlation are neglected.

Reference Height and Weights Used in Extrapolating Dietary Reference Intakes for Vitamins and Elements

The most up-to-date data providing heights and weights of individuals in the United States and Canada when the DRI process was initiated in 1995 were limited to anthropometric data from the 1988–1994 Third National Health and Nutrition Examination Survey (NHANES III) in the United States and older data from Canada. Reference values derived from the NHANES III data and used in

TABLE B-1 Reference Heights and Weights for Children and Adults in the United States Used in the Vitamin and Element Dietary Reference Intake Reports[a]

Sex	Age	Median Body Mass Index (kg/m^2)	Reference Height, cm (in)	Reference Weight[b] kg (lb)
Male, female	2–6 mo	—	64 (25)	7 (16)
	7–11 mo	—	72 (28)	9 (20)
	1–3 yr	—	91 (36)	13 (29)
	4–8 yr	15.8	118 (46)	22 (48)
Male	9–13 yr	18.5	147 (58)	40 (88)
	14–18 yr	21.3	174 (68)	64 (142)
	19–30 yr	24.4	176 (69)	76 (166)
Female	9–13 yr	18.3	148 (58)	40 (88)
	14–18 yr	21.3	163 (64)	57 (125)
	19–30 yr	22.8	163 (64)	61 (133)

[a] IOM (1997, 1998, 2000a, 2000b, 2001). Adapted from the Third National Health and Nutrition Examination Survey, 1988–1994.

[b] Calculated from body mass index and height for ages 4 through 8 years and older.

previous reports are given in Table B-1. Given the increasing prevalence of obesity in adults and children (DHHS, 1996), use of such population data is of concern. Thus recent data providing heights and body mass indexes (BMIs) for adults (Kuczmarski et al., 2000) and new growth charts for infants and children have allowed the development of new reference heights and weights in this report that should more closely approximate actual weights based on low risk of chronic disease and adequate growth for children. These new values are used in this report when reference values are needed, and are discussed in Chapter 1 (see Table 1-1).

The earlier values were obtained as follows: the median heights for the life stage and gender groups through age 30 years were identified, and the median weights for these heights were based on reported median BMI for the same individuals. Since there is no evidence that weight should change as adults age if activity is maintained, the reference weights for adults aged 19 through 30 years were applied to all adult age groups.

The most recent nationally representative data available for Canadians (from the 1970–1972 Nutrition Canada Survey [Demirjian, 1980]) were also reviewed. In general, median heights of children

from 1 year of age in the United States were greater by 3 to 8 cm (≈ 1 to 2.5 in) than those of children of the same age in Canada measured two decades earlier (Demirjian, 1980). This difference could be partly explained by approximations necessary to compare the two data sets, but more likely by a continuation of the secular trend of increased heights for age noted in the Nutrition Canada Survey when it compared data from that survey with an earlier (1953) national Canadian survey (Pett and Ogilvie, 1956).

Similarly, median weights beyond age 1 year derived from the recent survey in the United States (NHANES III, 1988–1994) were also greater than those obtained from the older Canadian survey (Demirjian, 1980). Differences were greatest during adolescence, ranging from 10 to 17 percent higher. The differences probably reflect the secular trend of earlier onset of puberty (Herman-Giddens et al., 1997) rather than differences in populations. Calculations of BMI for young adults (e.g., a median of 22.6 for Canadian women compared with 22.8 for U.S. women) resulted in similar values, thus indicating greater concordance between the two surveys by adulthood.

The reference weights used in the previous DRI reports (IOM, 1997, 1998, 2000a, 2000b, 2001) were thus based on the most recent data set available from either country, with recognition that earlier surveys in Canada indicated shorter stature and lower weights during adolescence than did surveys in the United States.

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C

Predictions of Daily Water and Sodium Requirements

To generate estimates of water and sodium losses at different energy expenditure levels and thus work rates, the U.S. Army Research Institute of Environmental Medicine (USARIEM) model was adapted for the four levels of energy expenditure identified in the Dietary Reference Intakes report on energy expenditure (IOM, 2002/2005). The USARIEM Heat Strain model is an empirical model that includes an equation to predict sweating rate during work (Moran et al., 1995, Shapiro et al., 1995). This algorithm has been used in the past to prepare military guidance for water needs during training and deployment.

The following is a description of the application of the model:

- Variables
  - Water requirements (L/d)
  - Sodium requirements (g/d)
- Prediction ranges
- Four energy expenditure levels (1,900; 2,400; 2,900; and 3,600 kcal/d)
- Temperature ranges (15°–40°C)

ANALYSIS

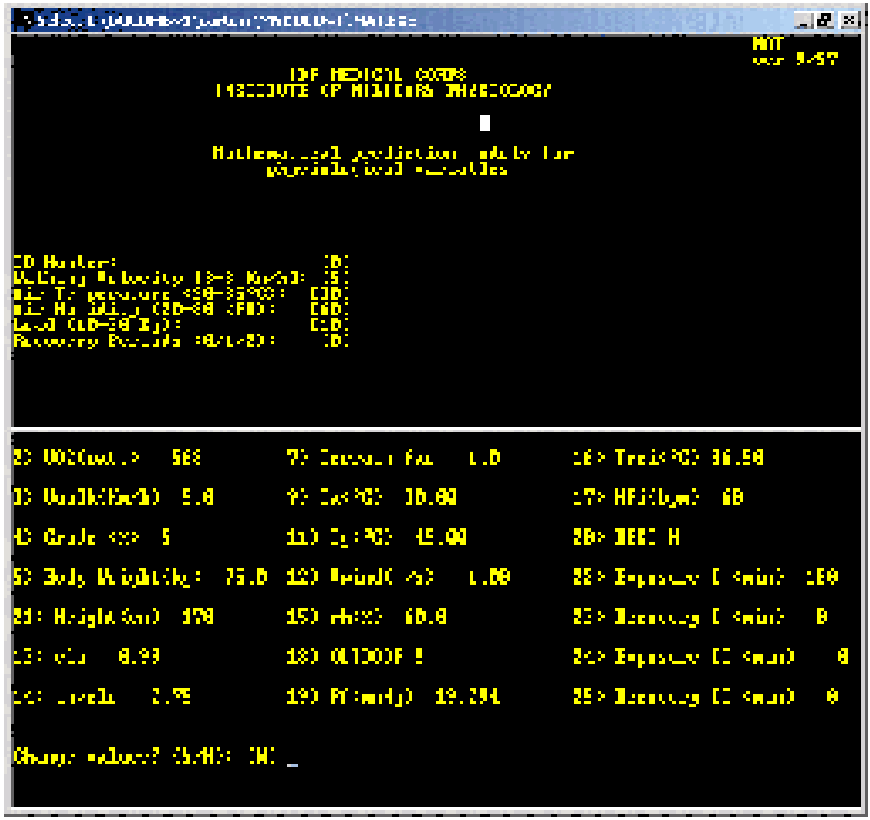
As shown in the example, the environmental, physiological, and individual information was inputted into the model. For any given individual, physiological, or environmental condition, the model predicted expected water losses. These data were then put into an

Excel 4.0 spreadsheet and used to generate the dataset of estimated water and sodium requirements at varying energy expenditure levels and temperatures. Environmental and individual assumptions are listed below. These data were then plotted using Sigma Plot 9.0 to generate a graphical display.

ASSUMPTIONS

- Individual
  - 70-kg person
  - Height = 170 cm
  - Walking velocity = 5 km/h
  - 0% grade
  - Clothing = 1.0 (cotton)
- Environmental
  - Partly cloudy day
  - Wind speed = 1 m/sec
  - Relative humidity = 50%
  - Outdoor
  - Water vapor pressure = 19.094 mm Hg
  - Load = 0 kg
  - Dry bulb temperature = 30°C
  - Black globe temperature = 45°C
- Physiological
  - Skin body temperature = 35.0°C
  - Rectal body temperature = 36.5°C
  - Initial heart rate = 60 bpm
  - Rest (N)
  - Exposure I = 720 min (= 12 h)
  - Exposure II = 720 min (= 12 h)
  - Exposure III (min) = 0
  - Exposure IV (min) = 0
- 1.0 L/d minimal requirements for survival:
- Sodium concentration of sweat (≈ 35 mmol/L), that of a partially acclimated person

Example (not used in this analysis):



The version of the program used was MAT version 9/97. Figures C-1a and C-1b describe the approximate daily water (Figure C-1a) and sodium (Figure C-1b) lost due to sweating as a function of dry bulb temperature and level of physical activity derived from modeling data (Table C-1).

*The screen is an example of the input variable capabilities; however, actual data are not presented in the database.

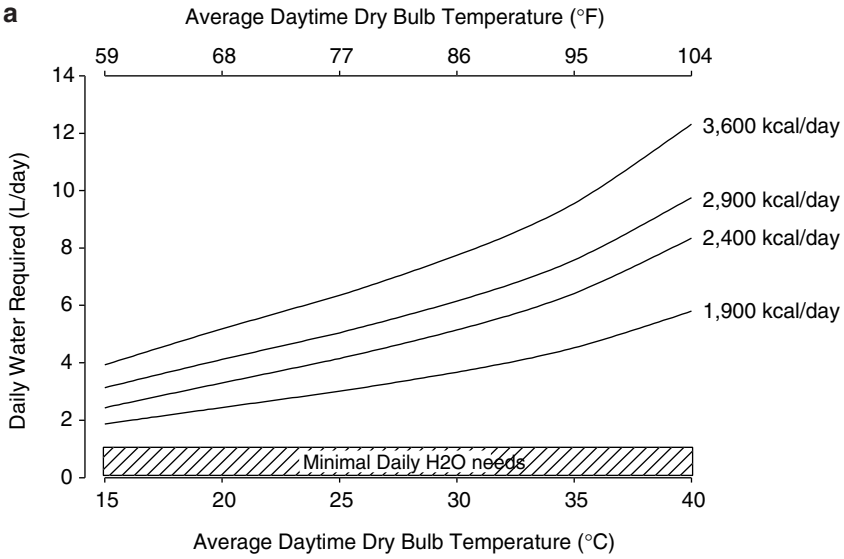


FIGURE C-1 Approximate daily water (Figure C-1a) and sodium (Figure C-1b) lost due to sweating as a function of dry bulb temperature and level of physical activity derived from modeling data (Table C-1). The hatched area indicates ≈ 1 L minimal water requirements. The y-axis represents the predicted water requirements that increase because of increased sweat losses to enable thermoregulation. The x-axis is the average daytime dry bulb temperature. The four lines represent the four levels of energy (in kcal/day) used in the model (1,900 kcal; 2,400 kcal; 2,900 kcal; and 3,600 kcal).

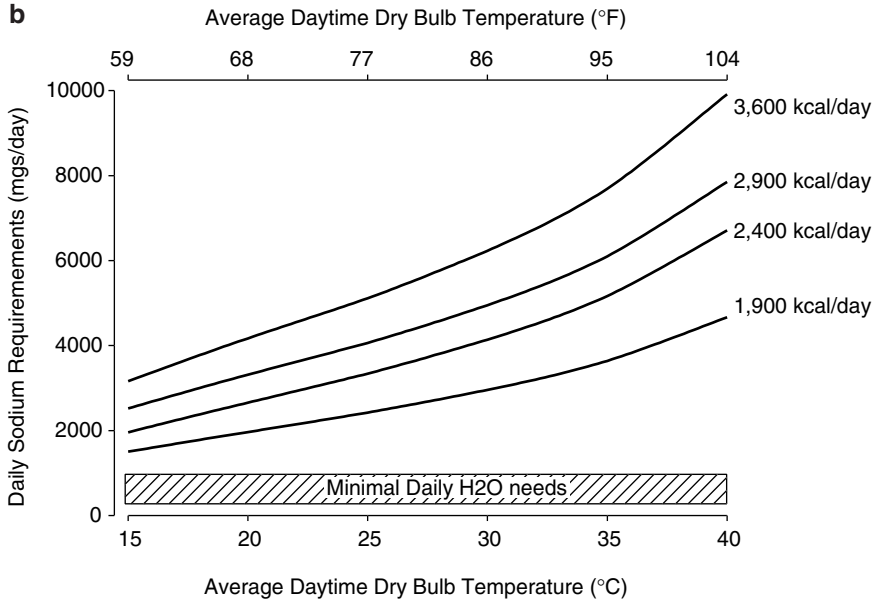


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TABLE C-1 Generated Database from the USARIEM Prediction Model

Given:	kcal/h	watts	per 12 h (kcal)
Rest	76	88	912
Light	234	273	2,808
Mod	382	444	4,582
Hard	531	618	6,372

Assumption: 1.0 liter water essential (daily resp water loss and kidney loss)

Predicted Sweating Rates (mL/h)

Air Tdb	Rh	Rest	Light	Mod	Hard
10	50	32	100	355	628
15	50	65	204	456	722
20	50	108	339	618	911
25	50	151	473	763	1,069
30	50	201	629	938	1,263
35	50	265	829	1,168	1,524
40	50	361	1,129	1,524	1,934

12 h Air	Scenario Rest	Light	Mod	Hard	Kcal	Water Loss
10	0.95	0.05	0	0	1,006.8	425
15	0.95	0.05	0	0	1,006.8	867
20	0.95	0.05	0	0	1,006.8	1,440
25	0.95	0.05	0	0	1,006.8	2,009
30	0.95	0.05	0	0	1,006.8	2,672
35	0.95	0.05	0	0	1,006.8	3,522
40	0.95	0.05	0	0	1,006.8	4,796

WBGT	Rest	Light	Mod	Hard	Kcal	Water Loss
9.9	0.7	0.25	0.05	0	1,570	782
14.2	0.7	0.25	0.05	0	1,570	1,434
18.8	0.7	0.25	0.05	0	1,570	2,299
23.1	0.7	0.25	0.05	0	1,570	3,148
27.4	0.7	0.25	0.05	0	1,570	4,141
31.7	0.7	0.25	0.05	0	1,570	5,416
36.2	0.7	0.25	0.05	0	1,570	7,336

Hard	A:J13
khard	A:E7
klight	A:E5
kmod	A:E6
krest	A:E4
light	A:H13
mod	A:I13
Rest	A:G13
sr	A:E13.I20
WBGT	A:F13

ttl kcal	ttl water loss			
1,918.8	1.4	35	23	1,147
1,918.8	2.4	35	23	1,905
1,918.8	2.9	35	23	2,367
1,918.8	3.5	35	23	2,825
1,918.8	4.2	35	23	3,358
1,918.8	5.0	35	23	4,042
1,918.8	6.3	35	23	5,068

ttl kcal	ttl water loss			
2,481.5	2.3	35	23	1,837
2,481.5	2.9	35	23	2,362
2,481.5	3.8	35	23	3,058
2,481.5	4.6	35	23	3,742
2,481.5	5.6	35	23	4,541
2,481.5	6.9	35	23	5,568
2,481.5	8.8	35	23	7,113

continued

TABLE C-1 Continued

WBGT	Rest	Light	Mod	Hard	Kcal	Water Loss
9.9	0.65	0.15	0.15	0.05	2,020	1,445
14.2	0.65	0.15	0.15	0.05	2,020	2,130
18.8	0.65	0.15	0.15	0.05	2,020	3,115
23.1	0.65	0.15	0.15	0.05	2,020	4,047
27.4	0.65	0.15	0.15	0.05	2,020	5,148
31.7	0.65	0.15	0.15	0.05	2,020	6,578
36.2	0.65	0.15	0.15	0.05	2,020	8,754
WBGT	Rest	Light	Mod	Hard	Kcal	Water Loss
9.9	0.45	0.25	0.2	0.1	2,666	2,078
14.2	0.45	0.25	0.2	0.1	2,666	2,925
18.8	0.45	0.25	0.2	0.1	2,666	4,179
23.1	0.45	0.25	0.2	0.1	2,666	5,350
27.4	0.45	0.25	0.2	0.1	2,666	6,741
31.7	0.45	0.25	0.2	0.1	2,666	8,552
36.2	0.45	0.25	0.2	0.1	2,666	11,316

ttl kcal	ttl water loss			
2,931.9	2.9	35	23	2,371
2,931.9	3.6	35	23	2,922
2,931.9	4.6	35	23	3,715
2,931.9	5.5	35	23	4,465
2,931.9	6.6	35	23	5,352
2,931.9	8.1	35	23	6,503
2,931.9	10.3	35	23	8,254

ttl kcal	ttl water loss			
3,578	3.6	35	23	2,881
3,578	4.4	35	23	3,562
3,578	5.7	35	23	4,572
3,578	6.9	35	23	5,515
3,578	8.2	35	23	6,634
3,578	10.1	35	23	8,091
3,578	12.8	35	23	10,317

D

U.S. Dietary Intake Data from the Third National Health and Nutrition Examination Survey, 1988–1994

TABLE D-1 Mean and Selected Percentiles for Usual Daily Intake of *Total* Water (mL): United States, NHANES III, 1988–1994

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 2–6 mo	784	1,112	443	607	707
Both sexes, 7–12 mo	809	1,324	525	768	861
Both sexes, 1–3 y	3,172	1,420	509	701	822
Both sexes, 4–8 y	3,247	1,779	1,069	1,235	1,332
Standard error		26	160	128	109
M, 9–13 y	1,188	2,535	1,211	1,495	1,669
Standard error		54	121	110	101
M, 14–18 y	891	3,400	1,765	2,118	2,333
Standard error		88	303	269	242
M, 19–30 y	1,872	3,908	1,849	2,260	2,517
Standard error		65	140	130	121
M, 31–50 y	2,495	3,848	1,632	2,094	2,380
Standard error		57	63	58	55
M, 51–70 y	1,872	3,551	1,606	2,024	2,281
Standard error		64	74	55	54
M, 71+ y	1,186	2,994	1,422	1,768	1,979
Standard error		45	64	53	46
F, 9–13 y	1,181	2,240	1,003	1,268	1,429
Standard error		49	70	61	58
F, 14–18 y	937	2,498	957	1,270	1,466
Standard error		66	80	74	74

25th	50th	75th	90th	95th	99th
856	1,047	1,313	1,564	1,786	2,384
1,051	1,260	1,544	1,833	2,027	2,588
1,032	1,320	1,703	2,141	2,492	3,238
1,513	1,742	2,005	2,274	2,453	2,826
76	35	49	130	200	389
2,001	2,439	2,964	3,523	3,901	4,715
82	61	77	143	200	342
2,743	3,282	3,928	4,617	5,086	6,102
180	100	150	337	488	858
3,019	3,709	4,577	5,548	6,232	7,763
101	73	88	181	267	493
2,920	3,632	4,527	5,574	6,340	8,122
50	54	78	128	178	325
2,765	3,387	4,148	5,018	5,643	7,065
56	58	91	129	187	424
2,377	2,895	3,502	4,136	4,559	5,453
35	34	64	116	158	260
1,734	2,132	2,623	3,181	3,582	4,497
52	47	65	96	139	312
1,841	2,331	2,958	3,722	4,301	5,688
70	52	80	172	287	673

continued

TABLE D-1 Continued

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
F, 19–30 y	1,885	2,838	1,034	1,399	1,628
Standard error		41	64	55	48
F, 31–50 y	2,906	3,101	1,202	1,589	1,829
Standard error		43	56	52	46
F, 51–70 y	2,002	3,024	1,281	1,649	1,877
Standard error		49	96	56	49
F, 71+ y	1,317	2,617	1,227	1,540	1,729
Standard error		35	70	59	52
Pregnant	341	3,118	1,363	1,692	1,904
Standard error		139	183	146	151
Lactating	98	3,791	1,600	2,173	2,500
Standard error		171	233	214	207
P/L	434	3,277	1,527	1,924	2,163
Standard error		122	183	167	157
All individuals	27,744	3,006	968	1,343	1,589
Standard error		24	16	21	19
All individuals (+P/L)	28,178	3,011	971	1,347	1,594
Standard error		24	15	22	19

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Total water intake reflects the sum of plain drinking (tap) water and the water content of all foods and beverages consumed. Data are limited to individuals who provided a valid response to the question "How much plain drinking water do you usually drink in a 24-hour period? Include only plain tap or spring water," and who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method to provide estimates of usual intake. Means, standard errors, and percentiles were ob-

25th	50th	75th	90th	95th	99th
2,077	2,687	3,435	4,244	4,795	5,979
39	40	60	99	133	219
2,280	2,898	3,690	4,582	5,276	7,038
34	46	48	82	127	325
2,316	2,898	3,594	4,333	4,832	5,899
56	50	93	94	139	391
2,082	2,536	3,064	3,609	3,969	4,715
41	34	52	90	122	196
2,341	2,966	3,736	4,530	5,053	6,167
161	200	201	272	309	835
3,076	3,753	4,463	5,127	5,537	6,333
199	194	193	222	261	371
2,610	3,182	3,839	4,511	4,953	5,869
139	130	155	225	288	446
2,087	2,791	3,662	4,659	5,423	7,247
21	34	37	51	79	143
2,093	2,797	3,667	4,662	5,423	7,235
21	37	38	51	80	143

tained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy or lactating status data or who responded "I don't know" to questions on pregnancy or lactating status were excluded from the analysis.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics (2003).

TABLE D-2 Mean and Selected Percentiles for Usual Daily Intake of Drinking Water (mL): United States, NHANES III, 1988–1994

Sex/Age Category[a]	*n*	Mean	Percentile		
			1st	5th	10th
Both sexes, 2–6 mo	784	115	0	0	0
Both sexes, 7–12 mo	809	172	0	0	0
Both sexes, 1–3 y	3,172	383	0	0	0
Both sexes, 4–8 y	3,247	615	120	203	261
Standard error		21	6	9	10
M, 9–13 y	1,188	1,096	67	191	292
Standard error		53	15	23	28
M, 14–18 y	891	1,393	64	215	346
Standard error		57	16	27	31
M, 19–30 y	1,872	1,389	43	165	282
Standard error		49	7	14	18
M, 31–50 y	2,495	1,292	34	146	255
Standard error		42	4	10	14
M, 51–70 y	1,872	1,255	43	171	289
Standard error		49	6	14	19
M, 71+ y	1,186	1,208	76	234	361
Standard error		45	11	18	22
F, 9–13 y	1,181	1,015	49	153	244
Standard error		48	12	20	23
F, 14–18 y	937	1,130	24	65	234
Standard error		50	6	28	76
F, 19–30 y	1,885	1,156	26	121	221
Standard error		34	4	12	17
F, 31–50 y	2,906	1,229	26	121	222
Standard error		24	2	8	11
F, 51–70 y	2,002	1,276	42	188	318
Standard error		35	8	17	21
F, 71+ y	1,317	1,122	62	218	343
Standard error		27	11	18	21
Pregnant	341	1,414	140	323	464
Standard error		98	149	173	174
Lactating	98	1,557	250	502	672
Standard error		136	254	237	213
P/L	434	1,442	119	305	449
Standard error		75	29	40	52
All individuals	27,744	1,139	26	122	218
Standard error		17	1	5	7
All individuals (+P/L)	28,178	1,144	27	124	221
Standard error		16	1	5	7

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a valid response to the question "How much plain drinking water do you usually drink in a 24-hour period? Include only plain tap or spring water," and who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method to provide estimates of usual intake. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jack-

25th	50th	75th	90th	95th	99th
0	59	148	237	473	887
0	118	237	473	473	946
118	237	473	946	1,183	1,892
382	558	786	1,041	1,218	1,607
13	18	27	41	53	86
530	918	1,471	2,132	2,607	3,670
37	49	68	98	125	196
659	1,173	1,889	2,728	3,325	4,652
37	45	69	131	190	344
580	1,106	1,894	2,867	3,581	5,208
24	37	65	116	160	276
537	1,031	1,767	2,671	3,333	4,835
22	32	54	102	147	267
578	1,055	1,715	2,480	3,020	4,217
27	39	62	105	143	238
647	1,075	1,626	2,230	2,640	3,509
31	43	59	86	109	167
465	838	1,372	2,014	2,481	3,548
29	40	63	103	139	236
467	924	1,557	2,391	2,757	4,262
58	50	101	156	134	285
484	941	1,596	2,373	2,931	4,179
24	32	45	74	103	181
492	974	1,692	2,571	3,212	4,666
17	23	32	57	85	163
621	1,099	1,742	2,467	2,968	4,041
29	37	46	64	82	131
617	1,017	1,511	2,036	2,386	3,120
25	28	33	46	58	93
774	1,246	1,873	2,582	3,078	4,160
157	116	143	306	450	802
1,011	1,468	2,005	2,558	2,920	3,666
164	139	214	364	484	764
773	1,267	1,922	2,661	3,175	4,298
72	70	113	159	213	416
466	905	1,560	2,366	2,956	4,294
11	16	22	34	47	83
470	911	1,567	2,373	2,961	4,296
11	15	22	34	47	82

knife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy or lactating status data or who responded "I don't know" to questions on pregnancy or lactating status were excluded from the analysis.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics (2003).

TABLE D-3 Mean and Selected Percentiles for Usual Daily Intake of Drinking and Beverage Water (mL): United States, NHANES III, 1988–1994

Sex/Age Category[a]	*n*	Mean	Percentile		
			1st	5th	10th
Both sexes, 2–6 mo	784	873	59	303	475
Both sexes, 7–12 mo	809	932	163	335	516
Both sexes, 1–3 y	3,172	1,007	237	399	479
Both sexes, 4–8 y	3,247	1,264	663	803	879
Standard error		28	90	83	68
M, 9–13 y	1,188	1,923	736	975	1,126
Standard error		54	65	68	70
M, 14–18 y	891	2,716	1,222	1,551	1,748
Standard error		78	252	219	192
M, 19–30 y	1,872	3,176	1,268	1,628	1,859
Standard error		67	94	92	89
M, 31–50 y	2,495	3,089	1,054	1,466	1,729
Standard error		59	85	76	77
M, 51–70 y	1,872	2,761	1,000	1,350	1,572
Standard error		60	54	51	49
M, 71+ y	1,186	2,212	834	1,123	1,304
Standard error		44	47	41	38
F, 9–13 y	1,181	1,709	635	833	961
Standard error		46	60	55	51
F, 14–18 y	937	2,015	532	832	1,023
Standard error		61	67	61	59
F, 19–30 y	1,885	2,321	678	1,025	1,235
Standard error		39	65	62	62
F, 31–50 y	2,906	2,523	791	1,107	1,315
Standard error		40	37	30	31
F, 51–70 y	2,002	2,392	782	1,121	1,335
Standard error		45	47	45	45
F, 71+ y	1,317	1,959	723	981	1,142
Standard error		33	43	41	40
Pregnant	341	2,445	898	1,189	1,378
Standard error		123	145	155	158
Lactating	98	3,058	2,058	2,342	2,496
Standard error		171	1,150	852	684
P/L	434	2,597	981	1,315	1,526
Standard error		110	126	119	115
All individuals	27,744	2,376	590	906	1,108
Standard error		24	15	15	16
All individuals (+P/L)	28,178	2,380	592	909	1,111
Standard error		24	15	15	15

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Plain drinking and beverage water intake reflects the sum of plain drinking (tap) water and the water content of all beverages consumed (including water from foods reported in a beverage combination). Data are limited to individuals who provided a valid response to the question "How much plain drinking water do you usually drink in a 24-hour period? Include only plain tap or spring water," and who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method to provide

25th	50th	75th	90th	95th	99th
649	848	1,054	1,308	1,495	2,019
684	886	1,125	1,419	1,592	2,083
673	906	1,262	1,638	1,918	2,545
1,028	1,226	1,448	1,705	1,860	2,251
56	38	33	86	109	232
1,421	1,822	2,315	2,850	3,217	4,016
69	58	64	99	143	286
2,113	2,587	3,171	3,840	4,325	5,434
141	95	129	302	460	877
2,321	2,970	3,802	4,750	5,427	6,976
80	68	86	158	228	422
2,231	2,883	3,705	4,694	5,426	7,114
79	65	79	132	189	349
2,002	2,576	3,307	4,174	4,812	6,286
50	56	77	121	164	291
1,651	2,113	2,665	3,248	3,640	4,467
33	36	60	105	142	233
1,220	1,587	2,063	2,608	3,000	3,904
43	43	65	109	147	247
1,371	1,828	2,454	3,236	3,827	5,218
49	49	78	178	274	538
1,601	2,152	2,876	3,625	4,163	5,369
66	39	92	120	140	338
1,728	2,303	3,062	3,987	4,688	6,384
32	37	58	78	138	432
1,741	2,254	2,883	3,617	4,145	5,320
45	50	59	97	119	196
1,453	1,868	2,365	2,892	3,245	3,994
37	34	42	73	101	172
1,757	2,287	2,957	3,709	4,243	5,457
148	141	157	270	403	805
2,758	3,054	3,353	3,625	3,789	4,100
404	184	370	659	843	1,200
1,933	2,477	3,130	3,821	4,289	5,288
111	115	142	200	255	405
1,528	2,146	2,954	3,908	4,623	6,442
17	21	33	43	66	128
1,532	2,151	2,959	3,912	4,625	6,436
18	22	31	42	62	125

estimates of usual intake. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy or lactating status data or who responded "I don't know" to questions on pregnancy or lactating status were excluded from the analysis.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics (2003).

TABLE D-4 Mean and Selected Percentiles for Usual Daily Intake of Food Water (mL): United States, NHANES III, 1988–1994

Sex/Age Category[a]	*n*	Mean	Percentile		
			1st	5th	10th
Both sexes, 2–6 mo	784	240	0	0	0
Both sexes, 7–12 mo	809	392	6	83	128
Both sexes, 1–3 y	3,172	414	55	121	159
Both sexes, 4–8 y	3,247	521	230	301	342
Standard error		10	7	8	9
M, 9–13 y	1,188	609	264	339	385
Standard error		20	49	44	38
M, 14–18 y	891	689	346	426	474
Standard error		25	119	102	89
M, 19–30 y	1,872	732	279	384	447
Standard error		16	11	21	29
M, 31–50 y	2,495	761	264	372	439
Standard error		13	22	21	19
M, 51–70 y	1,872	788	257	372	444
Standard error		17	26	26	25
M, 71+ y	1,186	777	247	352	419
Standard error		21	24	25	27
F, 9–13 y	1,181	531	278	339	375
Standard error		10	66	57	49
F, 14–18 y	937	488	183	250	290
Standard error		21	37	34	31
F, 19–30 y	1,885	515	230	296	335
Standard error		9	43	37	33
F, 31–50 y	2,906	574	175	261	314
Standard error		10	11	10	10
F, 51–70 y	2,002	631	228	316	370
Standard error		11	15	14	13
F, 71+ y	1,317	656	266	361	417
Standard error		11	32	28	24
Pregnant	341	666	236	329	386
Standard error		31	21	21	22
Lactating	98	723	251	350	412
Standard error		60	27	35	41
P/L	434	672	382	453	495
Standard error		29	166	140	122
All individuals	27,744	629	203	294	349
Standard error		4	10	9	8
All individuals (+P/L)	28,178	630	205	295	350
Standard error		4	10	9	8

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Food water intake reflects the water content of all foods consumed (excluding water from foods reported in a beverage combination). Data are limited to individuals who provided a valid response to the question "How much plain drinking water do you usually drink in a 24-hour period? Include only plain tap or spring water," and who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method to provide estimates of usual intake. Means, standard errors, and percentiles were ob-

25th	50th	75th	90th	95th	99th
31	189	354	553	723	1,119
236	347	493	651	861	1,296
260	379	522	694	841	1,183
416	507	609	717	790	944
9	9	11	14	17	29
469	579	715	870	982	1,241
28	17	33	73	108	201
562	673	798	923	1,004	1,170
61	29	53	113	156	253
563	707	873	1,049	1,167	1,417
30	17	26	37	37	50
566	731	924	1,121	1,251	1,519
16	13	16	26	33	52
578	748	952	1,181	1,342	1,693
22	17	19	34	46	80
552	733	953	1,189	1,349	1,695
26	20	32	44	65	158
440	521	610	699	755	870
33	13	25	53	72	113
366	464	582	714	807	1,014
25	21	27	48	68	120
409	501	606	712	780	920
23	11	19	40	55	89
415	545	701	869	985	1,233
8	9	13	21	29	52
473	607	763	923	1,029	1,248
11	11	17	24	29	44
519	643	779	909	992	1,155
16	11	19	33	43	65
495	638	807	981	1,096	1,335
25	31	39	49	57	77
532	691	879	1,076	1,207	1,484
52	64	76	89	102	141
570	662	763	863	927	1,056
84	36	63	142	198	322
454	597	768	950	1,074	1,351
6	4	5	10	14	28
455	598	769	950	1,074	1,349
6	5	5	10	14	28

tained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy or lactating status data or who responded "I don't know" to questions on pregnancy or lactating status were excluded from the analysis.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics (2003).

TABLE D-5 Mean and Selected Percentiles for Usual Daily Intake of Potassium (mg): United States, NHANES III, 1988–1994

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Both sexes, 2–6 mo	793	995	339	506	591
Both sexes, 7–12 mo	827	1,543	521	736	878
Both sexes, 1–3 y	3,309	1,970	590	869	1,071
Both sexes, 4–8 y	3,448	2,189	1,576	1,741	1,832
Standard error		22	508	381	308
M, 9–13 y	1,219	2,622	1,335	1,653	1,836
Standard error		53	192	155	136
M, 14–18 y	909	3,125	2,319	2,533	2,653
Standard error		110	1,140	868	707
M, 19–30 y	1,902	3,374	2,270	2,554	2,715
Standard error		56	405	320	267
M, 31–50 y	2,533	3,432	1,505	1,954	2,215
Standard error		43	114	106	88
M, 51–70 y	1,942	3,314	1,252	1,733	2,022
Standard error		55	68	60	56
M, 71+ y	1,255	2,918	1,258	1,661	1,897
Standard error		45	107	85	80
F, 9–13 y	1,216	2,243	1,182	1,454	1,608
Standard error		60	50	83	88
F, 14–18 y	949	2,120	796	1,086	1,264
Standard error		67	106	112	109
F, 19–30 y	1,901	2,233	1,310	1,547	1,681
Standard error		31	206	163	136
F, 31–50 y	2,939	2,489	1,170	1,483	1,669
Standard error		39	94	81	73
F, 51–70 y	2,065	2,506	1,120	1,451	1,646
Standard error		30	67	54	47
F, 71+ y	1,368	2,407	954	1,294	1,498
Standard error		42	65	58	53
F, Pregnant	346	2,905	1,245	1,617	1,843
Standard error		143	382	340	305
F, Lactating	99	3,636	1,304	1,984	2,355
Standard error		255	952	755	682
P/L	440	3,056	1,502	1,881	2,104
Standard error		131	511	416	352
All individuals	28,575	2,705	1,107	1,461	1,677
Standard error		19	33	29	29
All individuals (+P/L)	29,015	2,712	1,106	1,461	1,678
Standard error		19	33	30	30

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating status data or who responded "I don't know" to questions on pregnancy and lactating status were

25th	50th	75th	90th	95th	99th
715	913	1,156	1,487	1,729	2,432
1,122	1,448	1,859	2,326	2,653	3,301
1,426	1,869	2,427	2,951	3,344	4,474
1,992	2,178	2,375	2,561	2,676	2,901
177	28	160	328	434	647
2,161	2,555	3,007	3,489	3,820	4,535
100	55	104	180	250	441
2,862	3,108	3,370	3,619	3,775	4,081
416	115	399	803	1,070	1,610
3,000	3,343	3,714	4,073	4,300	4,751
168	60	148	309	417	646
2,697	3,321	4,037	4,779	5,291	6,430
72	48	54	104	161	262
2,547	3,190	3,938	4,757	5,323	6,543
51	54	79	86	115	304
2,321	2,836	3,423	4,042	4,459	5,337
69	44	54	98	153	329
1,879	2,206	2,565	2,925	3,160	3,647
74	58	80	97	101	180
1,602	2,041	2,553	3,080	3,426	4,142
90	70	98	135	160	261
1,921	2,208	2,518	2,815	3,002	3,372
86	33	72	150	204	319
2,009	2,429	2,898	3,380	3,704	4,395
57	41	54	86	116	201
2,000	2,435	2,932	3,452	3,803	4,549
37	31	41	74	100	186
1,873	2,343	2,873	3,399	3,738	4,420
45	41	54	84	108	164
2,268	2,814	3,442	4,083	4,504	5,377
230	151	224	433	598	979
2,970	3,645	4,310	4,901	5,252	5,911
524	269	384	599	665	760
2,507	3,001	3,545	4,077	4,416	5,095
227	123	255	472	623	942
2,073	2,598	3,212	3,871	4,328	5,311
27	21	22	32	44	82
2,077	2,604	3,221	3,883	4,341	5,329
26	21	21	31	43	78

excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics (2003).

TABLE D-6 Mean and Selected Percentiles for Usual Daily Intake of Potassium (mg) by Non-Hispanic Whites: United States, NHANES III, 1988–1994

Sex/Age Category[a]	*n*	Mean	Percentile		
			1st	5th	10th
Both sexes, 2–6 mo	444	988	317	537	599
Both sexes, 7–12 mo	459	1,595	627	780	933
Both sexes, 1–3 y	1,012	1,959	697	908	1,084
Both sexes, 4–8 y	929	2,173	1,397	1,597	1,711
Standard error		33	27	28	29
M, 9–13 y	309	2,672	1,246	1,556	1,746
Standard error		84	74	65	62
M, 14–18 y	224	3,189	1,263	1,665	1,916
Standard error		169	87	100	111
M, 19–30 y	456	3,515	1,545	1,989	2,258
Standard error		81	61	57	56
M, 31–50 y	852	3,545	1,697	2,117	2,370
Standard error		54	54	46	44
M, 51–70 y	899	3,416	1,635	2,046	2,292
Standard error		70	64	54	57
M, 71+ y	870	3,026	1,468	1,853	2,077
Standard error		56	71	68	101
F, 9–13 y	315	2,195	946	1,245	1,422
Standard error		66	52	49	50
F, 14–18 y	273	2,122	874	1,151	1,320
Standard error		79	57	59	61
F, 19–30 y	541	2,238	968	1,274	1,454
Standard error		35	33	30	30
F, 31–50 y	1,008	2,605	1,191	1,518	1,714
Standard error		42	42	37	36
F, 51–70 y	949	2,575	1,282	1,596	1,779
Standard error		35	39	50	61
F, 71+ y	973	2,430	1,204	1,506	1,681
Standard error		46	41	39	40
Pregnant	83	2,875	1,276	1,690	1,927
Standard error		162	143	146	148
Lactating	19	3,878	1,652	2,267	2,602
Standard error		401	788	599	508
P/L	101	2,995	1,302	1,743	1,995
Standard error		145	145	141	138
All individuals	10,513	2,788	1,159	1,525	1,744
Standard error		24	17	17	18
All individuals (+P/L)	10,614	2,792	1,160	1,527	1,746
Standard error		24	17	18	19

[a] M = male, F = female, P/L = female pregnant and/or lactating.

NOTES: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating status data or who responded "I don't know" to questions on pregnancy and lactating status were

25th	50th	75th	90th	95th	99th
712	901	1,146	1,477	1,736	2,547
1,176	1,479	1,910	2,413	2,842	3,301
1,444	1,859	2,406	2,905	3,316	4,063
1,912	2,152	2,411	2,660	2,816	3,127
30	33	38	45	50	63
2,106	2,577	3,134	3,719	4,112	4,943
63	75	102	144	181	278
2,401	3,047	3,822	4,645	5,201	6,389
135	168	207	257	301	422
2,760	3,405	4,151	4,914	5,414	6,449
60	73	100	138	169	246
2,841	3,444	4,139	4,850	5,317	6,288
45	51	65	90	113	178
2,748	3,327	3,987	4,656	5,093	5,994
58	66	90	113	159	361
2,474	2,948	3,488	4,069	4,469	5,326
112	53	102	114	111	314
1,745	2,146	2,591	3,031	3,312	3,876
55	65	83	117	148	226
1,638	2,050	2,527	3,016	3,338	4,006
68	78	94	117	139	195
1,784	2,190	2,640	3,082	3,364	3,927
31	33	43	65	85	135
2,077	2,536	3,058	3,583	3,924	4,623
35	39	50	69	86	129
2,107	2,510	2,970	3,451	3,776	4,470
52	39	76	63	82	324
1,998	2,387	2,816	3,237	3,504	4,039
42	46	52	63	72	95
2,346	2,842	3,368	3,865	4,172	4,770
153	162	183	222	257	345
3,194	3,863	4,544	5,167	5,543	6,255
369	317	459	726	925	1,350
2,439	2,964	3,515	4,033	4,352	4,972
136	143	164	196	222	284
2,148	2,677	3,304	3,971	4,430	5,451
20	23	28	37	46	75
2,151	2,681	3,308	3,974	4,431	5,447
20	22	29	37	46	75

excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics (2003).

TABLE D-7 Mean and Selected Percentiles for Usual Daily Intake of Potassium (mg) by Non-Hispanic Blacks: United States, NHANES III, 1988–1994

Sex/Age Category[a]	*n*	Mean	Percentile		
			1st	5th	10th
Both sexes, 2–6 mo	156	974	339	488	545
Both sexes, 7–12 mo	128	1,378	375	701	832
Both sexes, 1–3 y	980	1,862	371	713	921
Both sexes, 4–8 y	1,105	2,170	1,345	1,556	1,676
Standard error		28	24	22	22
M, 9–13 y	425	2,386	1,018	1,325	1,511
Standard error		59	47	48	49
M, 14–18 y	326	2,991	1,029	1,428	1,681
Standard error		103	70	74	76
M, 19–30 y	586	3,107	1,171	1,582	1,851
Standard error		137	98	144	146
M, 31–50 y	808	2,887	1,164	1,539	1,769
Standard error		59	59	53	72
M, 51–70 y	489	2,369	917	1,232	1,426
Standard error		78	57	53	52
M, 71+ y	191	2,183	838	1,118	1,293
Standard error		91	61	55	53
F, 9–13 y	431	2,114	892	1,186	1,360
Standard error		62	48	45	47
F, 14–18 y	333	2,062	843	1,123	1,292
Standard error		68	43	47	51
F, 19–30 y	652	2,063	801	1,075	1,244
Standard error		59	39	42	44
F, 31–50 y	1,003	2,063	866	1,131	1,294
Standard error		35	31	30	29
F, 51–70 y	530	2,063	863	1,136	1,301
Standard error		33	34	31	30
F, 71+ y	217	2,014	872	1,135	1,293
Standard error		76	43	49	54
Pregnant	111	2,816	1,236	1,579	1,789
Standard error		174	141	135	135
Lactating	11	3,437	1,525	1,525	1,562
P/L	120	2,874	1,262	1,612	1,827
Standard error		166	130	126	128
All individuals	8,360	2,334	888	1,206	1,375
Standard error		21	18	18	19
All individuals (+P/L)	8,480	2,343	891	1,211	1,382
Standard error		21	18	19	19

[a] M = male, F = female, P/L = female pregnant and/or lactating.

NOTES: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months, children 1–3 years of age, and lactating females are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating status data or who responded "I don't know" to questions on pregnancy and lactating status

25th	50th	75th	90th	95th	99th
694	929	1,173	1,568	1,698	2,030
983	1,312	1,668	2,117	2,406	2,619
1,307	1,793	2,331	2,865	3,314	4,317
1,890	2,146	2,424	2,693	2,863	3,200
24	28	33	41	47	60
1,861	2,310	2,828	3,358	3,706	4,425
54	60	69	84	100	143
2,176	2,841	3,642	4,493	5,068	6,293
80	93	130	202	265	428
2,383	3,036	3,686	4,386	4,936	6,269
199	341	134	291	291	614
2,206	2,778	3,450	4,148	4,611	5,578
68	66	121	102	132	500
1,795	2,278	2,844	3,430	3,819	4,629
56	69	95	132	162	233
1,632	2,083	2,625	3,201	3,588	4,416
57	75	117	188	247	398
1,678	2,069	2,501	2,923	3,192	3,728
53	64	74	86	95	122
1,607	2,004	2,454	2,905	3,197	3,790
60	70	81	97	112	155
1,566	1,986	2,476	2,980	3,313	4,008
50	58	70	89	106	155
1,599	1,994	2,451	2,920	3,228	3,870
30	33	44	65	85	134
1,610	2,003	2,451	2,902	3,195	3,797
30	32	42	62	80	127
1,587	1,958	2,381	2,806	3,082	3,644
64	77	92	112	129	174
2,188	2,712	3,331	3,979	4,413	5,327
144	168	205	254	293	395
1,869	2,985	5,268	5,268	5,454	5,454
2,234	2,768	3,398	4,057	4,496	5,422
138	161	196	240	275	364
1,734	2,230	2,808	3,433	3,810	4,779
19	22	33	68	61	69
1,744	2,238	2,823	3,429	3,816	4,808
18	19	29	42	44	70

were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics (2003).

TABLE D-8 Mean and Selected Percentiles for Usual Daily Intake of Sodium (mg): United States, NHANES III, 1988–1994

Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Both sexes, 2–6 mo	793	282	78	117	137
Both sexes, 7–12 mo	827	846	150	198	239
Both sexes, 1–3 y	3,309	2,114	443	763	980
Both sexes, 4–8 y	3,448	2,864	1,680	1,980	2,150
Standard error		47	41	43	44
M, 9–13 y	1,219	3,809	2,123	2,533	2,771
Standard error		141	575	464	395
M, 14–18 y	909	4,598	2,332	2,873	3,193
Standard error		135	612	513	444
M, 19–30 y	1,902	4,746	3,464	3,802	3,991
Standard error		88	1,350	1,060	884
M, 31–50 y	2,533	4,418	1,928	2,498	2,830
Standard error		68	143	118	104
M, 51–70 y	1,942	3,781	1,851	2,323	2,595
Standard error		73	177	157	150
M, 71+ y	1,255	3,198	1,284	1,738	2,007
Standard error		63	143	106	92
F, 9–13 y	1,216	3,178	1,732	2,092	2,295
Standard error		79	65	63	64
F, 14–18 y	949	3,083	1,075	1,494	1,757
Standard error		114	145	137	130
F, 19–30 y	1,901	3,159	1,908	2,225	2,404
Standard error		66	388	319	275
F, 31–50 y	2,939	3,032	1,416	1,797	2,017
Standard error		50	126	103	91
F, 51–70 y	2,065	2,613	1,117	1,471	1,680
Standard error		33	87	75	66
F, 71+ y	1,368	2,395	827	1,177	1,392
Standard error		54	82	87	81
Pregnant	346	3,522	2,084	2,448	2,656
Standard error		129	1,070	848	706
Lactating	99	3,697	2,522	2,834	3,009
Standard error		300	1,590	1,200	971
P/L	440	3,581	2,095	2,478	2,695
Standard error		103	626	507	431
All individuals	28,575	3,415	1,174	1,672	1,956
Standard error		31	47	44	38
All individuals (+P/L)	29,015	3,418	1,177	1,675	1,959
Standard error		31	46	43	37

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating status data or who responded "I don't know" to questions on pregnancy and lactating status were

25th	50th	75th	90th	95th	99th
178	234	303	418	595	1,398
341	645	1,202	1,746	2,095	2,899
1,410	1,953	2,617	3,403	4,141	5,374
2,452	2,818	3,225	3,636	3,906	4,471
45	48	52	59	65	80
3,198	3,724	4,325	4,950	5,373	6,277
268	146	243	508	718	1,220
3,777	4,504	5,317	6,127	6,648	7,707
306	153	246	504	689	1,100
4,323	4,717	5,137	5,539	5,791	6,289
548	132	433	969	1,330	2,080
3,452	4,271	5,220	6,187	6,841	8,283
95	72	108	167	225	373
3,079	3,672	4,359	5,100	5,612	6,721
120	72	104	203	277	455
2,496	3,103	3,793	4,508	4,983	5,979
70	59	103	161	221	424
2,654	3,097	3,610	4,160	4,542	5,396
71	81	93	117	137	189
2,266	2,941	3,746	4,592	5,156	6,345
117	116	156	237	304	469
2,721	3,107	3,538	3,978	4,271	4,888
188	84	123	294	425	723
2,425	2,946	3,540	4,146	4,558	5,478
73	56	57	96	140	263
2,062	2,535	3,077	3,644	4,024	4,828
50	35	41	77	110	193
1,794	2,294	2,863	3,504	3,978	5,064
64	53	72	114	176	366
3,028	3,478	3,968	4,443	4,744	5,343
435	143	393	804	1,080	1,640
3,315	3,674	4,054	4,414	4,637	5,076
581	301	667	1,190	1,540	2,230
3,081	3,543	4,039	4,516	4,816	5,407
283	120	219	459	624	969
2,494	3,219	4,123	5,121	5,815	7,413
33	30	41	66	94	161
2,499	3,223	4,126	5,120	5,813	7,405
32	30	40	65	91	153

excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics (2003).

TABLE D-9 Mean and Selected Percentiles for Usual Daily Intake of Sodium (mg) by Non-Hispanic Whites: United States, NHANES III, 1988–1994

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 2–6 mo	444	268	74	117	137
Both sexes, 7–12 mo	459	831	157	211	249
Both sexes, 1–3 y	1,012	2,097	495	791	1,030
Both sexes, 4–8 y	929	2,818	1,567	1,862	2,036
Standard error		56	44	45	47
M, 9–13 y	309	3,900	1,844	2,284	2,554
Standard error		184	110	113	117
M, 14–18 y	224	4,648	1,977	2,598	2,971
Standard error		194	142	146	152
M, 19–30 y	456	4,905	2,176	2,779	3,146
Standard error		120	100	95	96
M, 31–50 y	852	4,422	2,087	2,621	2,942
Standard error		79	68	61	61
M, 51–70 y	899	3,812	1,889	2,356	2,628
Standard error		74	64	82	110
M, 71+ y	870	3,382	1,564	2,004	2,261
Standard error		79	65	59	64
F, 9–13 y	315	3,148	1,547	1,897	2,110
Standard error		111	87	82	82
F, 14–18 y	273	3,018	1,220	1,622	1,867
Standard error		138	74	90	101
F, 19–30 y	541	3,090	1,389	1,782	2,015
Standard error		62	40	48	54
F, 31–50 y	1,008	3,005	1,385	1,765	1,991
Standard error		55	48	46	46
F, 51–70 y	949	2,676	1,248	1,601	1,806
Standard error		41	36	61	73
F, 71+ y	973	2,484	1,178	1,493	1,678
Standard error		60	51	50	51
Pregnant	83	3,544	1,667	2,132	2,403
Standard error		181	186	176	171
Lactating	19	3,741	2,113	2,460	2,671
Standard error		411	310	309	316
P/L	101	3,583	1,747	2,198	2,460
Standard error		141	184	165	157
All individuals	10,513	3,434	1,217	1,707	1,995
Standard error		36	20	23	24
All individuals (+P/L)	10,614	3,436	1,221	1,711	2,000
Standard error		36	20	23	24

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTES: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating status data or who responded "I don't know" to questions on pregnancy and lactating status were

25th	50th	75th	90th	95th	99th
175	222	301	397	546	1,237
346	593	1,212	1,744	2,115	2,590
1,412	1,954	2,554	3,293	4,061	5,303
2,357	2,759	3,215	3,677	3,977	4,596
50	56	64	76	87	116
3,071	3,753	4,566	5,430	6,017	7,288
131	162	223	319	401	617
3,660	4,527	5,504	6,479	7,108	8,386
169	196	229	265	291	355
3,840	4,740	5,790	6,877	7,598	9,107
103	121	144	177	205	285
3,539	4,299	5,171	6,059	6,641	7,842
68	81	97	116	131	172
3,115	3,707	4,390	5,125	5,630	6,718
117	70	94	110	129	356
2,724	3,294	3,943	4,614	5,060	5,996
67	73	100	126	152	276
2,514	3,041	3,665	4,322	4,763	5,702
81	89	122	199	283	540
2,328	2,920	3,601	4,297	4,752	5,688
120	141	162	185	204	258
2,441	2,980	3,616	4,302	4,775	5,808
53	57	81	107	162	411
2,408	2,931	3,522	4,115	4,497	5,277
48	53	64	80	94	128
2,171	2,611	3,107	3,625	3,974	4,713
67	39	73	88	84	165
2,014	2,425	2,882	3,357	3,679	4,379
54	57	70	93	113	191
2,892	3,486	4,133	4,758	5,153	5,937
166	174	210	282	344	496
3,074	3,612	4,267	4,978	5,465	6,527
341	391	475	603	715	1,020
2,935	3,518	4,161	4,793	5,194	5,997
147	145	157	189	222	310
2,532	3,250	4,135	5,106	5,785	7,297
28	34	45	58	70	103
2,537	3,254	4,136	5,104	5,781	7,286
28	35	45	59	70	104

excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small so, their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics (2003).

TABLE D-10 Mean and Selected Percentiles for Usual Daily Intake of Sodium (mg) by Non-Hispanic Blacks: United States, NHANES III, 1988–1994

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 2–6 mo	156	303	74	111	134
Both sexes, 7–12 mo	128	810	128	196	198
Both sexes, 1–3 y	980	2,370	490	865	1,069
Both sexes, 4–8 y	1,105	3,100	1,647	1,989	2,192
Standard error		51	44	40	40
M, 9–13 y	425	3,519	1,575	2,009	2,273
Standard error		125	100	177	233
M, 14–18 y	326	4,604	1,832	2,420	2,785
Standard error		174	123	134	141
M, 19–30 y	586	4,831	1,907	2,537	2,927
Standard error		179	86	98	108
M, 31–50 y	808	4,307	1,752	2,339	2,689
Standard error		116	66	71	76
M, 51–70 y	489	3,136	1,173	1,594	1,855
Standard error		140	78	196	264
M, 71+ y	191	2,517	954	1,302	1,515
Standard error		89	54	59	64
F, 9–13 y	431	3,277	1,451	1,879	2,134
Standard error		110	83	77	77
F, 14–18 y	333	3,220	1,295	1,728	1,991
Standard error		143	162	141	131
F, 19–30 y	652	3,359	1,346	1,766	2,029
Standard error		112	49	68	78
F, 31–50 y	1,003	2,971	1,285	1,689	1,926
Standard error		50	47	43	42
F, 51–70 y	530	2,447	1,021	1,351	1,550
Standard error		63	46	49	51
F, 71+ y	217	2,040	831	1,094	1,255
Standard error		91	65	68	71
Pregnant	111	3,845	1,631	2,164	2,479
Standard error		265	237	226	226
Lactating	11	3,960	1,087	1,087	1,264
P/L	120	3,836	1,609	2,139	2,453
Standard error		235	212	202	201
All individuals	8,360	3,376	1,043	1,561	1,858
Standard error		36	23	31	30
All individuals (+P/L)	8,480	3,384	1,047	1,566	1,864
Standard error		36	23	32	30

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTES: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months, children 1–3 years of age, and lactating females are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating status data or who responded "I don't know" to questions on pregnancy and lactating status

25th	50th	75th	90th	95th	99th
166	244	312	417	530	2,486
295	512	1,166	1,816	2,025	2,997
1,569	2,195	2,901	3,899	4,615	5,807
2,564	3,032	3,562	4,096	4,444	5,157
42	49	61	79	95	135
2,768	3,406	4,147	4,911	5,415	6,464
242	126	181	238	234	494
3,486	4,412	5,513	6,671	7,447	9,089
154	173	211	283	349	526
3,670	4,644	5,788	6,976	7,766	9,421
131	165	220	303	372	550
3,332	4,145	5,100	6,127	6,832	8,358
89	110	144	188	223	309
2,351	3,004	3,779	4,588	5,125	6,246
277	137	185	226	207	608
1,917	2,432	3,025	3,627	4,020	4,827
76	91	110	133	152	203
2,604	3,194	3,861	4,528	4,958	5,829
86	107	137	172	198	260
2,485	3,117	3,844	4,583	5,065	6,056
122	130	157	201	240	344
2,536	3210	4,019	4,877	5,457	6,698
86	97	140	206	265	448
2,352	2878	3,485	4,131	4,572	5,515
42	47	62	86	107	162
1,918	2382	2,905	3,427	3,764	4,448
55	62	74	92	108	149
1,563	1964	2,434	2,922	3,246	3,924
77	88	107	141	172	255
3,054	3765	4,548	5,316	5,803	6,778
235	257	290	337	377	485
1,615	2724	4,993	8,362	8,362	8,362
3,031	3748	4,545	5,331	5,833	6,840
207	226	257	303	343	449
2,412	3,170	4,134	5,127	5,828	7,563
26	32	60	71	86	133
2,419	3179	4,144	5,138	5,838	7,564
26	32	59	72	86	133

were excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics (2003).

TABLE D-11 Mean and Selected Percentiles for Usual Daily Intake of Sodium:Potassium (molar ratio): United States, NHANES III, 1988–1994

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 2–6 mo	793	0.49	0.20	0.27	0.31
Both sexes, 7–12 mo	827	0.93	0.22	0.31	0.36
Both sexes, 1–3 y	3,309	1.99	0.49	0.77	0.94
Both sexes, 4–8 y	3,448	2.39	1.54	1.74	1.86
Standard error		0.04	0.03	0.03	0.03
M, 9–13 y	1,219	2.63	1.44	1.71	1.88
Standard error		0.06	0.04	0.04	0.04
M, 14–18 y	909	2.81	1.37	1.75	1.96
Standard error		0.05	0.06	0.05	0.05
M, 19–30 y	1,902	2.56	1.37	1.66	1.82
Standard error		0.02	0.03	0.03	0.03
M, 31–50 y	2,533	2.35	1.24	1.50	1.65
Standard error		0.03	0.04	0.03	0.03
M, 51–70 y	1,942	2.14	1.09	1.34	1.48
Standard error		0.03	0.03	0.03	0.02
M, 71+ y	1,255	2.07	1.04	1.29	1.43
Standard error		0.04	0.03	0.03	0.03
F, 9–13 y	1,216	2.74	1.48	1.77	1.94
Standard error		0.09	0.06	0.04	0.07
F, 14–18 y	949	2.70	1.43	1.71	1.88
Standard error		0.07	0.05	0.05	0.05
F, 19–30 y	1,901	2.61	1.36	1.65	1.82
Standard error		0.04	0.03	0.03	0.03
F, 31–50 y	2,939	2.27	1.18	1.43	1.57
Standard error		0.04	0.03	0.03	0.03
F, 51–70 y	2,065	1.96	1.02	1.24	1.37
Standard error		0.02	0.02	0.02	0.02
F, 71+ y	1,368	1.89	0.99	1.20	1.32
Standard error		0.04	0.02	0.02	0.03
Pregnant	346	2.32	1.16	1.42	1.57
Standard error		0.14	0.07	0.11	0.12
Lactating	99	2.03	1.06	1.23	1.36
Standard error		0.25	0.09	0.11	0.13
P/L	440	2.27	1.14	1.39	1.55
Standard error		0.13	0.06	0.08	0.10
All individuals	28,575	2.32	1.20	1.46	1.61
Standard error		0.01	0.01	0.01	0.01
All individuals (+P/L)	29,015	2.32	1.08	1.36	1.53
Standard error		0.01	0.01	0.01	0.01

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTES: Data are limited to individuals who provided a complete and reliable 24-hour dietary recall on Day 1. The intake distributions for infants 2–6 and 7–12 months and children 1–3 years of age are unadjusted. Means and percentiles for these groups were computed using SAS PROC UNIVARIATE. For all other groups, data were adjusted using the Iowa State University method. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Infants and children fed human milk and females who had "blank but applicable" pregnancy and lactating status data or who responded "I don't know" to questions on pregnancy and lactating status were

25th	50th	75th	90th	95th	99th
0.37	0.43	0.50	0.64	0.75	1.96
0.45	0.76	1.23	1.75	2.11	3.26
1.29	1.81	2.42	3.14	3.71	5.74
2.08	2.35	2.65	2.97	3.18	3.62
0.03	0.04	0.04	0.05	0.06	0.08
2.18	2.57	3.01	3.47	3.78	4.41
0.05	0.06	0.07	0.09	0.11	0.15
2.33	2.74	3.21	3.72	4.09	4.91
0.05	0.05	0.07	0.10	0.12	0.17
2.13	2.50	2.93	3.35	3.63	4.18
0.02	0.02	0.03	0.04	0.05	0.07
1.93	2.28	2.70	3.12	3.41	4.06
0.04	0.03	0.04	0.04	0.05	0.09
1.74	2.07	2.45	2.86	3.15	3.82
0.02	0.02	0.04	0.07	0.10	0.21
1.69	2.00	2.37	2.78	3.07	3.71
0.03	0.03	0.04	0.08	0.11	0.19
2.26	2.66	3.11	3.62	4.00	4.94
0.11	0.08	0.18	0.20	0.19	0.25
2.20	2.62	3.10	3.61	3.95	4.66
0.05	0.06	0.08	0.11	0.14	0.24
2.14	2.54	3.00	3.49	3.83	4.55
0.03	0.04	0.05	0.06	0.08	0.11
1.84	2.20	2.61	3.05	3.34	3.99
0.03	0.04	0.05	0.08	0.09	0.12
1.61	1.91	2.25	2.60	2.84	3.36
0.02	0.02	0.03	0.03	0.04	0.06
1.55	1.84	2.18	2.52	2.75	3.21
0.03	0.04	0.05	0.06	0.07	0.11
1.87	2.25	2.69	3.16	3.47	4.12
0.13	0.13	0.16	0.22	0.27	0.44
1.61	1.94	2.33	2.78	3.11	3.95
0.16	0.21	0.30	0.48	0.66	1.21
1.83	2.19	2.61	3.08	3.41	4.13
0.10	0.11	0.15	0.21	0.27	0.50
1.89	2.25	2.67	3.12	3.42	4.09
0.01	0.01	0.02	0.02	0.03	0.05
1.84	2.23	2.71	3.22	3.57	4.36
0.01	0.02	0.02	0.02	0.03	0.05

excluded from all analyses. Females who were both pregnant and lactating were included in both the Pregnant and Lactating categories. The sample sizes for the Pregnant and Lactating categories were very small, so their estimates of usual intake distributions are not reliable.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics (2003).

E

U.S. Dietary Intake Data for Water and Weaning Foods from the Continuing Survey of Food Intakes by Individuals, 1994–1996, 1998

TABLE E-1 Mean and Selected Percentiles for Daily Intake of Total Water (g): United States, CSFII, 1994–1996, 1998

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	595	1,007	425	544	655
Both sexes, 7–12 mo	526	1,259	560	751	836
Both sexes, 1–3 y	3,897	1,355	457	655	765
Both sexes, 4–8 y	3,857	1,561	531	766	904
M, 9–13 y	586	2,037	686	942	1,103
M, 14–18 y	471	2,791	695	1,070	1,308
M, 19–30 y	915	3,361	767	1,275	1,558
M, 31–50 y	1,800	3,189	937	1,392	1,652
M, 51–70 y	1,674	2,883	900	1,267	1,539
M, 71+ y	715	2,449	768	1,100	1,351
F, 9–13 y	597	1,744	584	818	964
F, 14–18 y	447	2,021	591	821	997
F, 19–30 y	805	2,367	653	933	1,188
F, 31–50 y	1,686	2,475	705	1,088	1,270
F, 51–70 y	1,600	2,457	834	1,161	1,375
F, 71+ y	667	2,166	784	1,022	1,259
P/L	124	2,775	781	1,049	1,305
All individuals	20,838	2,486	649	953	1,151
All individuals (+P/L)	20,962	2,489	650	954	1,151

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Total water intake reflects the sum of plain drinking water and the water content of all foods and beverages consumed.

25th	50th	75th	90th	95th	99th
785	947	1,157	1,433	1,661	2,139
995	1,182	1,466	1,764	1,939	2,520
984	1,279	1,627	2,016	2,289	3,096
1,138	1,454	1,825	2,373	2,737	3,577
1,417	1,900	2,439	3,099	3,806	5,042
1,778	2,439	3,316	4,467	5,532	8,526
2,127	2,948	3,976	5,699	7,017	11,319
2,169	2,835	3,836	5,032	6,011	9,024
2,057	2,641	3,460	4,380	5,178	7,800
1,827	2,325	2,980	3,585	3,951	5,056
1,229	1,608	2,121	2,660	3,130	4,486
1,368	1,846	2,374	3,119	4,008	5,663
1,548	2,129	2,795	3,862	4,576	6,984
1,702	2,257	2,946	3,826	4,507	6,605
1,819	2,310	2,908	3,637	4,273	5,634
1,567	2,062	2,628	3,229	3,706	5,137
1,909	2,682	3,497	4,269	4,974	6,861
1,574	2,210	3,025	4,050	4,950	7,444
1,576	2,213	3,035	4,057	4,950	7,440

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service, Continuing Survey of Food Intakes by Individuals (CSFII), 1994–1996, 1998.

SOURCE: ENVIRON International Corporation (2002).

TABLE E-2 Mean and Selected Percentiles for Daily Intake of Drinking Water (g): United States, CSFII, 1994–1996, 1998

Sex/Age Category[a]	*n*	Mean	Percentile		
			1st	5th	10th
Both sexes, 0–6 mo	595	53	0	0	0
Both sexes, 7–12 mo	526	113	0	0	0
Both sexes, 1–3 y	3,897	281	0	0	0
Both sexes, 4–8 y	3,857	422	0	0	0
M, 9–13 y	586	602	0	0	0
M, 14–18 y	471	854	0	0	0
M, 19–30 y	915	1,052	0	0	0
M, 31–50 y	1,800	890	0	0	0
M, 51–70 y	1,674	825	0	0	0
M, 71+ y	715	798	0	0	0
F, 9–13 y	597	509	0	0	0
F, 14–18 y	447	679	0	0	0
F, 19–30 y	805	777	0	0	0
F, 31–50 y	1,686	799	0	0	0
F, 51–70 y	1,600	841	0	0	89
F, 71+ y	667	814	0	0	177
P/L	124	1,015	0	0	0
All individuals	20,838	759	0	0	0
All individuals (+P/L)	20,962	762	0	0	0

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a 24-hour dietary recall on Day 1 and provided a valid response to the question "How many fluid ounces of plain drinking water, that is, tap water or any bottled water that is not carbonated, with nothing added to it, did you drink yesterday?"

25th	50th	75th	90th	95th	99th
0	0	59	177	237	473
0	30	148	355	473	946
59	237	414	710	887	1,419
118	296	532	946	1,183	1,892
237	473	946	1,419	1,892	2,602
237	473	946	1,892	2,366	5,677
237	710	1,419	2,366	3,548	7,570
237	591	1,183	1,892	2,366	4,731
237	710	1,183	1,892	2,070	3,785
296	710	1,065	1,892	1,892	2,839
148	355	710	1,183	1,508	2,898
177	473	946	1,479	1,892	3,785
177	473	946	1,892	2,366	4,731
237	532	1,065	1,892	2,247	3,785
296	710	1,183	1,892	1,892	3,785
473	710	1,035	1,656	1,892	2,839
237	946	1,892	2,129	2,691	3,548
237	473	946	1,892	2,129	3,785
237	473	946	1,892	2,129	3,785

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service, Continuing Survey of Food Intakes by Individuals (CSFII), 1994–1996, 1998.
SOURCE: ENVIRON International Corporation (2002).

TABLE E-3 Mean and Selected Percentiles for Daily Intake of Drinking and Beverage Water (g): United States, CSFII, 1994–1996, 1998

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	595	927	320	488	568
Both sexes, 7–12 mo	526	935	291	423	535
Both sexes, 1–3 y	3,897	930	219	336	442
Both sexes, 4–8 y	3,857	1,050	221	400	505
M, 9–13 y	586	1,439	296	491	665
M, 14–18 y	471	2,105	321	660	795
M, 19–30 y	915	2,650	442	798	1,022
M, 31–50 y	1,800	2,441	470	828	1,019
M, 51–70 y	1,674	2,129	435	727	995
M, 71+ y	715	1,712	397	665	819
F, 9–13 y	597	1,232	318	451	571
F, 14–18 y	447	1,502	286	458	659
F, 19–30 y	805	1,850	330	567	757
F, 31–50 y	1,686	1,919	429	679	823
F, 51–70 y	1,600	1,847	354	713	884
F, 71+ y	667	1,564	341	636	788
P/L	124	2,083	443	654	872
All individuals	20,838	1,871	326	566	710
All individuals (+P/L)	20,962	1,874	327	566	710

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a 24-h dietary recall on Day 1 and provided a valid response to the question "How many fluid ounces of plain drinking water, that is, tap water or any bottled water that is not carbonated, with nothing added to it, did you drink yesterday?"

25th	50th	75th	90th	95th	99th
726	858	1,072	1,352	1,553	2,139
671	881	1,136	1,418	1,599	2,199
625	858	1,149	1,475	1,748	2,430
683	946	1,289	1,641	2,002	2,827
915	1,335	1,764	2,378	2,765	3,852
1,230	1,716	2,554	3,619	4,678	7,530
1,504	2,194	3,243	4,883	6,181	10,614
1,516	2,101	3,016	4,203	5,188	8,224
1,358	1,858	2,580	3,529	4,214	6,812
1,166	1,621	2,129	2,676	3,050	4,267
774	1,070	1,547	2,062	2,465	4,004
931	1,354	1,838	2,515	2,956	4,264
1,079	1,595	2,261	3,190	4,007	6,370
1,186	1,730	2,328	3,175	3,824	5,900
1,240	1,655	2,241	2,961	3,528	4,975
1,065	1,418	1,940	2,533	2,839	3,785
1,190	1,829	2,668	3,626	4,406	6,195
1,057	1,593	2,308	3,273	4,132	6,637
1,060	1,595	2,311	3,281	4,132	6,613

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service, Continuing Survey of Food Intakes by Individuals (CSFII), 1994–1996, 1998.

SOURCE: ENVIRON International Corporation (2002).

TABLE E-4 Mean and Selected Percentiles for Daily Intake of Food Water (g): United States, CSFII, 1994–1996, 1998

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
Both sexes, 0–6 mo	595	80	0	0	0
Both sexes, 7–12 mo	526	324	0	36	85
Both sexes, 1–3 y	3,897	424	54	124	173
Both sexes, 4–8 y	3,857	511	87	163	214
M, 9–13 y	586	598	92	178	235
M, 14–18 y	471	686	90	184	245
M, 19–30 y	915	711	94	194	270
M, 31–50 y	1,800	748	92	212	295
M, 51–70 y	1,674	755	102	237	314
M, 71+ y	715	737	81	233	306
F, 9–13 y	597	512	89	148	200
F, 14–18 y	447	519	47	121	172
F, 19–30 y	805	517	55	134	171
F, 31–50 y	1,686	556	49	140	195
F, 51–70 y	1,600	610	99	178	251
F, 71+ y	667	602	69	188	262
P/L	124	692	108	219	262
All individuals	20,838	614	51	158	221
All individuals (+P/L)	20,962	615	52	158	222

[a] M = male, F = female, P/L = pregnant and/or lactating.
NOTE: Data are limited to individuals who provided a 24-h dietary recall on Day 1.

25th	50th	75th	90th	95th	99th
0	0	146	254	319	482
190	306	445	582	637	879
262	387	548	727	840	1,112
324	461	644	847	1,006	1,360
365	520	772	1,076	1,199	1,592
366	582	886	1,269	1,565	2,064
396	642	915	1,300	1,498	1,913
450	660	970	1,325	1,520	2,196
477	703	969	1,251	1,466	1,850
469	671	920	1,263	1,508	1,789
314	458	636	854	1,054	1,691
283	476	684	892	1,097	1,467
292	459	662	926	1,106	1,559
323	508	731	959	1,154	1,561
385	564	786	1,023	1,159	1,443
380	555	758	996	1,173	1,565
431	665	852	1,177	1,403	1,757
354	545	792	1,084	1,309	1,811
355	547	794	1,086	1,311	1,810

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service, Continuing Survey of Food Intakes by Individuals (CSFII), 1994–1996, 1998.
SOURCE: ENVIRON International Corporation (2002).

TABLE E-5 Mean Daily Intake of Sodium, Potassium, and Total Water from Weaning Foods by Breastfeeding Infants: United States, CSFII, 1994–1996, 1998

Age Category	*n*	Sodium (mg)	Potassium (mg)	Water (g)
7–12 mo	51	287	442	324
Standard error		61.3	42.8	34.5

NOTE: Sample population includes breastfeeding infants with two 24-hour diet recalls; infants consuming more than 62 g (approximately ¼ cup) fluid milk and/or infant formula on either of the survey days were not included in the analyses. Means and standard errors were calculated with WesVar Complex Samples 3.0. Total water intake reflects the sum of plain drinking water and the water content of all foods and beverages consumed. Data on plain drinking water intake was provided by a proxy in response to the question "How many fluid ounces of plain drinking water, that is, tap water or any bottled water that is not carbonated, with nothing added to it, did you drink yesterday?"

DATA SOURCE: U.S. Department of Agriculture, Agricultural Research Service, Continuing Survey of Food Intakes by Individuals (CSFII), 1994–1996, 1998.

SOURCE: ENVIRON International Corporation (2002).

F

Canadian Dietary Intake Data for Adults from Ten Provinces, 1990–1997

TABLE F-1 Mean and Selected Percentiles for Usual Daily Intake of Moisture (mg) by Adults: Canada, Ten Provinces, 1990–1999

			Percentile		
Sex/Age Category[a]	*n*	Mean	5th	10th	25th
M, 19–30 y	316	3,039	1,735	1,864	2,198
Standard error		124	79	80	78
M, 31–50 y	566	2,961	1,896	1,958	2,320
Standard error		79	55	38	68
M, 51–70 y	712	2,706	1,573	1,798	2,135
Standard error		87	126	66	48
M, 71+ y	424	2,394	1,574	1,691	1,937
Standard error		68	110	54	48
F, 19–30 y	371	2,455	1,313	1,463	1,856
Standard error		130	123	74	67
F, 31–50 y	857	2,553	1,495	1,608	1,934
Standard error		61	62	40	44
F, 51–70 y	842	2,406	1,458	1,624	1,866
Standard error		76	101	47	40
F, 71+ y	401	2,139	1,379	1,480	1,712
Standard error		83	75	55	41
All individuals (+P/L)	4,489	2,667	1,510	1,692	2,020
Standard error		37	42	27	23

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Variability estimated using SUDAAN V8.0.1, with Taylor linearization, taking into account the complex sample design. Adjustment for intra individual variability using modified NAS method (for method see Karpinski KF and Nargundkar MS. 1992. Nova Scotia nutrition survey methodology report. Report No. E451311-0010. Canada:

50th	75th	90th	95th
2,691	3,482	4,024	4,395
142	180	172	262
2,711	3,212	3,781	4,471
57	76	181	279
2,519	3,053	3,585	4,100
53	76	171	313
2,312	2,840	3,148	3,394
57	112	90	104
2,229	2,774	3,570	3,975
103	158	214	315
2,383	2,868	3,272	3,672
55	67	85	267
2,243	2,718	3,199	3,580
52	88	123	215
2,061	2,471	2,784	3,204
75	135	200	230
2,454	2,984	3,588	4,033
36	44	80	244

Health and Welfare Canada; Wright, J.D., Ervin B., and Briefel R.R., eds. 1994. Consensus workshop on dietary assessment: Nutrition monitoring and tracking the year 2000 objectives. Hyattsville, MD: U.S. Department of Health and Human Services).

SOURCE: Health Canada.

TABLE F-2 Mean and Selected Percentiles for Usual Daily Intake of Potassium (mg) by Adults: Canada, Ten Provinces, 1990–1999

			Percentile		
Sex/Age Category[a]	*n*	Mean	5th	10th	25th
M, 19–30 y	1,698	3,595	1,916	2,325	2,822
Standard error		96	140	78	40
M, 31–50 y	2,931	3,535	2,143	2,333	2,817
Standard error		62	121	61	40
M, 51–70 y	3,131	3,394	2,022	2,280	2,694
Standard error		71	131	61	46
M, 71+ y	885	3,287	1,959	2,175	2,651
Standard error		82	172	101	69
F, 19–30 y	1,851	2,561	1,449	1,650	1,983
Standard error		49	96	57	48
F, 31–50 y	3,539	2,695	1,596	1,793	2,169
Standard error		34	76	41	34
F, 51–70 y	3,322	2,714	1,634	1,846	2,186
Standard error		34	73	28	30
F, 71+ y	857	2,695	1,529	1,716	2,111
Standard error		94	93	84	73
All individuals (+P/L)	18,214	3,082	1,691	1,942	2,363
Standard error		21	51	21	19

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Variability estimated using SUDAAN V8.0.1, with Taylor linearization, taking into account the complex sample design. Adjustment for intra individual variability using modified NAS method (for method see Karpinski KF and Nargundkar MS. 1992. Nova Scotia nutrition survey methodology report. Report No. E451311-0010. Canada:

50th	75th	90th	95th
3,342	4,071	4,779	5,367
84	78	121	299
3,364	4,001	4,600	5,084
45	47	79	197
3,257	3,897	4,486	4,792
94	97	77	149
3,191	3,782	4,297	4,664
90	97	98	180
2,433	2,927	3,389	3,636
41	37	73	121
2,559	2,994	3,529	3,856
31	37	70	170
2,630	3,046	3,559	3,842
47	35	59	129
2,605	3,125	3,552	3,912
75	108	182	246
2,897	3,555	4,209	4,677
18	25	32	155

Health and Welfare Canada; Wright J.D., Ervin B., and Briefel R.R., eds. 1994. Consensus workshop on dietary assessment: Nutrition monitoring and tracking the year 2000 objectives. Hyattsville, MD: U.S. Department of Health and Human Services).

SOURCE: Health Canada.

TABLE F-3 Mean and Selected Percentiles for Usual Daily Intake of Sodium (mg) by Adults: Canada, Ten Provinces, 1990–1999

			Percentile		
Sex/Age Category[a]	*n*	Mean	5th	10th	25th
M, 19–30 y	1,698	4,029	2,340	2,625	3,074
Standard error		137	227	96	119
M, 31–50 y	2,931	3,710	2,080	2,343	2,868
Standard error		69	124	57	61
M, 51–70 y	3,131	3,377	1,830	2,091	2,562
Standard error		61	123	55	48
M, 71+ y	885	2,831	1,665	1,871	2,300
Standard error		81	123	94	103
F, 19–30 y	1,851	2,784	1,672	1,862	2,130
Standard error		71	100	39	33
F, 31–50 y	3,539	2,672	1,466	1,714	2,041
Standard error		48	75	35	29
F, 51–70 y	3,322	2,328	1,343	1,502	1,796
Standard error		40	72	36	41
F, 71+ y	857	2,197	1,177	1,420	1,680
Standard error		81	84	66	47
All individuals (+P/L)	18,214	3,120	1,572	1,811	2,236
Standard error		40	66	30	27

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Variability estimated using SUDAAN V8.0.1, with Taylor linearization, taking into account the complex sample design. Adjustment for intra individual variability using modified NAS method (for method see Karpinski KF and Nargundkar MS. 1992. Nova Scotia nutrition survey methodology report. Report No. E451311-0010. Canada:

50th	75th	90th	95th
3,774	4,464	5,161	5,829
91	133	167	309
3,447	4,125	4,822	5,154
45	75	77	197
3,142	3,765	4,530	4,996
33	45	108	232
2,763	3,210	3,700	3,969
59	55	96	165
2,517	2,922	3,510	3,799
36	74	111	174
2,436	2,968	3,448	3,746
41	65	67	150
2,152	2,562	3,037	3,429
44	29	68	201
1,977	2,502	2,868	3,188
70	102	161	238
2,792	3,573	4,330	4,887
37	45	66	240

Health and Welfare Canada; Wright, J.D., Ervin B., and Briefel R.R., eds. 1994. Consensus workshop on dietary assessment: Nutrition monitoring and tracking the year 2000 objectives. Hyattsville, MD: U.S. Department of Health and Human Services).

SOURCE: Health Canada.

G

U.S. Water Intake and Serum Osmolality Data from the Third National Health and Nutrition Examination Survey, 1988–1994

TABLE G-1 Estimates of Serum Osmolality by Decile of Mean Total Water Intake: United States, NHANES III, 1988–1994

Sex/Age Category[a]	Decile of Total Water Intake[b]	*n*	Total Water Intake (mL/d)		Serum Osmolality (mmol/kg)	
			Mean	Median	Mean	Median
M, 12–18 y	1	94	1,364	1,412	278	279
	2	87	1,837	1,857	279	281
	3	105	2,146	2,138	277	277
	4	81	2,489	2,492	278	279
	5	86	2,793	2,789	279	279
	6	82	3,128	3,149	279	278
	7	80	3,511	3,490	279	279
	8	57	3,953	3,948	278	279
	9	70	4,499	4,497	279	282
	10	96	6,460	5,877	281	281
M, 19–50 y	1	380	1,694	1,763	279	279
	2	336	2,322	2,339	279	278
	3	287	2,667	2,660	281	282
	4	278	2,984	2,974	280	281
	5	296	3,310	3,308	280	282
	6	307	3,691	3,692	280	279

TABLE G-1 Continued

Sex/Age Category[a]	Decile of Total Water Intake[b]	*n*	Total Water Intake (mL/d)		Serum Osmolality (mmol/kg)	
			Mean	Median	Mean	Median
	7	312	4,133	4,122	280	281
	8	276	4,727	4,689	280	280
	9	304	5,555	5,502	280	280
	10	315	7,934	7,279	280	281
M, 51–70 y	1	184	1,635	1,721	280	281
	2	146	2,168	2,149	282	283
	3	156	2,570	2,593	281	281
	4	134	2,907	2,894	281	281
	5	105	3,172	3,174	283	283
	6	125	3,465	3,469	281	282
	7	124	3,798	3,798	280	280
	8	119	4,319	4,337	280	280
	9	128	5,162	5,141	281	283
	10	95	7,203	6,721	281	282
M, 71+ y	1	106	1,444	1,523	283	283
	2	101	1,895	1,895	283	283
	3	83	2,208	2,216	283	284
	4	87	2,455	2,452	284	284
	5	74	2,707	2,715	283	284
	6	66	2,976	2,980	282	284
	7	68	3,218	3,225	281	281
	8	83	3,597	3,572	283	284
	9	67	4,129	4,151	283	283
	10	73	5,450	5,247	281	280
F, 12–18 y	1	103	943	942	278	279
	2	106	1,444	1,469	278	279
	3	81	1,696	1,685	276	276
	4	105	1,964	1,961	276	277
	5	105	2,202	2,173	276	276
	6	83	2,492	2,512	278	279
	7	100	2,719	2,711	278	279
	8	84	3,069	3,085	277	278
	9	104	3,737	3,672	278	279
	10	83	5,525	5,279	277	278
F, 19–50 y	1	429	1,249	1,315	277	277
	2	369	1,727	1,735	277	278
	3	350	2,033	2,015	277	278
	4	347	2,309	2,299	276	277
	5	347	2,612	2,603	277	278
	6	340	2,923	2,925	277	278
	7	320	3,270	3,257	277	277
	8	306	3,725	3,719	278	279

continued

TABLE G-1 Continued

Sex/Age Category[a]	Decile of Total Water Intake[b]	*n*	Total Water Intake (mL/d)		Serum Osmolality (mmol/kg)	
			Mean	Median	Mean	Median
	9	281	4,298	4,267	277	277
	10	353	6,163	5,426	277	278
F, 51–70 y	1	174	1,321	1,382	281	281
	2	135	1,836	1,854	280	281
	3	147	2,102	2,117	280	280
	4	130	2,388	2,406	280	281
	5	134	2,682	2,682	281	282
	6	151	2,969	2,971	280	281
	7	135	3,301	3,291	281	281
	8	127	3,704	3,720	280	279
	9	129	4,230	4,216	281	281
	10	141	5,807	5,331	279	280
F, 71+ y	1	110	1,191	1,242	282	283
	2	102	1,649	1,656	282	282
	3	101	1,957	1,953	282	282
	4	87	2,193	2,190	281	281
	5	79	2,382	2,378	283	283
	6	92	2,589	2,591	282	283
	7	84	2,883	2,882	283	282
	8	99	3,173	3,152	281	281
	9	79	3,599	3,601	280	281
	10	88	4,852	4,646	282	283

[a] M = male, F = female.

[b] Total water intake reflects the sum of drinking water and the water content of foods and beverages.

NOTE: Data are limited to individuals who provided a valid response to a question on usual plain drinking water intake, provided a complete and reliable 24-hour dietary recall, and had a serum osmolality measurement. Females who were pregnant, lactating, or had "blank but applicable" pregnancy or lactating status data or who responded "I don't know" to questions on pregnancy or lactating status were excluded from the analysis.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation (2002).

H

U.S. Total Water Intake Data by Frequency of Leisure Time Activity from the Third National Health and Nutrition Examination Survey, 1988–1994

TABLE H-1 Mean and Selected Percentiles for Usual Daily Intake of Total Water (g) by Frequency of Activity of Children: United States, NHANES III, 1988–1994

Frequency of Activity Sex/Age Category[a]	*n*	Mean	Percentile 1st	5th	10th
Less than once per week					
M, 8–16 y	35	2,205	1,173	1,386	1,517
Standard error		224	102	121	146
F, 8–16 y	106	1,965	875	1,050	1,165
Standard error		191	44	60	77
1–4 times per week					
M, 8–16 y	719	2,546	1,158	1,434	1,608
Standard error		62	36	40	44
F, 8–16 y	984	2,170	979	1,238	1,396
Standard error		57	36	35	37
5+ times per week					
M, 8–16 y	1,138	2,831	1,352	1,648	1,832
Standard error		72	52	54	60
F, 8–16 y	873	2,386	1,095	1,369	1,538
Standard error		60	41	42	45

[a] M = male, F = female.

NOTE: Data are limited to individuals who provided a valid response to a question on usual plain drinking water intake, provided a complete and reliable 24-hour dietary recall, and provided at least one valid response to questions on participation in leisure time exercise or physical activities. Participants reported the frequency of walking, jogging or running, bicycling or using an exercise bike, swimming, aerobics or aerobic dancing, other dancing, calisthenics or exercises, garden or yard work, and lifting weights in the past month. Four open-ended questions regarding other exercises, sports, or physically active hobbies (not mentioned above) were asked. Females who were

25th	50th	75th	90th	95th	99th
1,770	2,113	2,539	3,011	3,339	4,064
197	250	287	311	332	430
1,409	1,783	2,318	2,988	3,499	4,743
115	171	248	347	429	655
1,948	2,414	2,999	3,650	4,107	5,132
51	59	79	125	172	306
1,690	2,066	2,529	3,066	3,459	4,369
43	53	71	100	126	201
2,193	2,688	3,311	4,010	4,501	5,602
77	63	90	114	187	631
1,862	2,291	2,806	3,356	3,728	4,532
51	60	75	96	114	165

pregnant, lactating, or had "blank but applicable" pregnancy or lactating status data or who responded "I don't know" to questions on pregnancy or lactating status were excluded from the analysis. Total water intake reflects the sum of drinking water and the water content of all foods and beverages consumed.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation (2002).

TABLE H-2 Mean and Selected Percentiles for Usual Daily Intake of Total Water (g) by Frequency of Leisure Time Activity of Individuals 17 Years of Age and Older—No Activity: United States, NHANES III, 1988–1994

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
M, 17–18 y	17	2,342	1,135	1,619	1,860
M, 19–30 y	208	3,343	1,424	1,799	2,037
Standard error		119	78	76	78
M, 31–50 y	385	3,608	2,098	2,457	2,667
Standard error		117	659	564	495
M, 51–70 y	335	3,332	1,466	1,879	2,130
Standard error		138	194	179	172
M, 71+ y	295	2,660	1,178	1,483	1,673
Standard error		91	52	50	51
F, 17–18 y	43	1,972	439	1,027	1,027
F, 19–30 y	387	2,682	1,367	1,661	1,838
Standard error		124	289	255	231
F, 31–50 y	671	2,693	1,010	1,333	1,540
Standard error		90	121	130	143
F, 51–70 y	580	2,943	1,177	1,545	1,775
Standard error		84	113	101	93
F, 71+ y	534	2,451	926	1,241	1,437
Standard error		51	77	68	63
P/L	128	2,873	1,349	1,736	1,962
Standard error		219	184	204	220
All individuals (non-P/L)	3,455	2,923	1,090	1,463	1,698
Standard error		38	50	43	42
All individuals, y (+P/L)	3,583	2,924	1,094	1,465	1,700
Standard error		37	58	43	44

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a valid response to a question on usual plain drinking water intake, provided a complete and reliable 24-hour dietary recall, and provided at least one valid response to questions on participation in leisure time exercise or physical activities. Participants reported the frequency of walking, jogging or running, bicycling or using an exercise bike, swimming, aerobics or aerobic dancing, other dancing, calisthenics or exercises, garden or yard work, and lifting weights in the past month. Four open-ended questions regarding other exercises, sports, or physically active hobbies (not mentioned above) were asked. Females who were

25th	50th	75th	90th	95th	99th
1,907	2,041	3,167	3,371	3,371	3,956
2,506	3,155	3,971	4,885	5,529	6,982
90	114	155	244	334	594
3,054	3,538	4,085	4,639	5,000	5,745
346	152	262	609	867	1,460
2,605	3,220	3,936	4,677	5,168	6,194
162	156	173	248	330	554
2,041	2,536	3,144	3,804	4,258	5,248
58	80	122	188	244	387
1,081	1,898	2,324	3,003	3,287	4,331
2,171	2,602	3,105	3,629	3,978	4,713
184	142	196	353	485	804
1,951	2,524	3,249	4,059	4,629	5,899
137	88	131	173	242	644
2,219	2,812	3,522	4,277	4,788	5,882
83	87	116	169	215	332
1,816	2,328	2,954	3,627	4,082	5,052
55	53	72	124	172	292
2,337	2,740	3,239	3,924	4,476	5,827
231	224	293	376	454	771
2,150	2,743	3,488	4,366	5,007	6,473
37	42	55	86	113	201
2,151	2,744	3,490	4,366	5,004	6,462
42	42	60	84	112	236

pregnant, lactating, or had "blank but applicable" pregnancy or lactating status data or who responded "I don't know" to questions on pregnancy or lactating status were excluded from the analysis. Total water intake reflects the sum of drinking water and the water content of all foods and beverages consumed.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation (2002).

TABLE H-3 Mean and Selected Percentiles for Usual Daily Intake of Total Water (g) by Frequency of Leisure Time Activity of Individuals 17 Years of Age and Older—Between 0 and 5 Occasions per Week: United States, NHANES III, 1988–1994

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
M, 17–18 y	92	3,635	1,094	1,626	1,963
Standard error		273	166	211	244
M, 19–30 y	722	3,982	1,893	2,290	2,540
Standard error		112	213	198	186
M, 31–50 y	1,093	3,774	1,560	1,996	2,271
Standard error		83	89	79	80
M, 51–70 y	792	3,529	1,746	2,132	2,367
Standard error		86	162	147	135
M, 71+ y	386	2,939	1,454	1,806	2,015
Standard error		73	97	88	83
F, 17–18 y	148	2,469	892	1,212	1,412
Standard error		118	158	125	106
F, 19–30 y	853	2,682	1,077	1,419	1,631
Standard error		48	109	101	94
F, 31–50 y	1,402	3,028	1,284	1,630	1,849
Standard error		49	65	57	52
F, 51–70 y	777	2,924	1,275	1,619	1,833
Standard error		63	58	57	58
F, 71+ y	390	2,558	1,162	1,475	1,663
Standard error		53	69	52	45
P/L	191	3,191	1,355	1,730	1,965
Standard error		171	94	101	112
All individuals (non-P/L)	6,655	3,266	1,283	1,681	1,932
Standard error		37	38	34	32
All individuals (+P/L)	6,846	3,265	1,292	1,689	1,939
Standard error		37	37	32	30

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a valid response to a question on usual plain drinking water intake, provided a complete and reliable 24-hour dietary recall, and provided at least one valid response to questions on participation in leisure time exercise or physical activities. Participants reported the frequency of walking, jogging or running, bicycling or using an exercise bike, swimming, aerobics or aerobic dancing, other dancing, calisthenics or exercises, garden or yard work, and lifting weights in the past month. Four open-ended questions regarding other exercises, sports or physically active hobbies (not mentioned above) were asked. Females who were pregnant, lactating, or had "blank but applicable" pregnancy or lactating status data or

25th	50th	75th	90th	95th	99th
2,613	3,470	4,479	5,522	6,211	7,641
300	334	319	299	336	570
3,038	3,744	4,663	5,723	6,486	8,232
157	118	156	330	490	922
2,812	3,559	4,501	5,550	6,284	7,911
82	74	107	179	254	490
2,815	3,403	4,105	4,850	5,354	6,432
112	89	114	198	272	454
2,399	2,877	3,410	3,942	4,284	4,983
76	76	94	134	169	258
1,802	2,334	2,991	3,703	4,187	5,217
94	119	158	214	269	426
2,038	2,573	3,207	3,872	4,316	5,258
75	49	67	138	199	349
2,278	2,867	3,599	4,410	4,978	6,248
43	40	59	103	143	251
2,245	2,796	3,463	4,179	4,668	5,724
62	67	77	114	156	275
2,018	2,475	3,009	3,560	3,924	4,680
42	55	75	101	124	184
2,422	3,039	3,793	4,611	5,173	6,401
141	176	214	292	377	626
2,415	3,060	3,868	4,834	5,567	7,318
30	37	42	85	115	285
2,420	3,063	3,865	4,821	5,545	7,270
28	34	41	77	111	242

who responded "I don't know" to questions on pregnancy or lactating status were excluded from the analysis.

Frequency of activity per week was calculated from frequency of activity reported per month; the frequency reflects the sum of the frequencies calculated for each reported activity. Total water intake reflects the sum of drinking water and the water content of all foods and beverages consumed.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation (2002).

TABLE H-4 Mean and Selected Percentiles for Usual Daily Intake of Total Water (g) by Frequency of Leisure Time Activity of Individuals 17 Years of Age and Older—5 or More Occasions per Week: United States, NHANES III, 1988–1994

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
M, 17–18 y	245	3,499	1,659	2,040	2,277
Standard error		177	583	524	471
M, 19–30 y	941	3,929	1,937	2,363	2,624
Standard error		78	253	225	203
M, 31–50 y	1,017	3,961	1,851	2,277	2,542
Standard error		84	117	110	104
M, 51–70 y	745	3,609	1,676	2,062	2,302
Standard error		92	71	67	66
M, 71+ y	505	3,165	1,614	1,945	2,148
Standard error		74	77	70	67
F, 17–18 y	157	2,863	1,021	1,412	1,655
Standard error		196	326	316	306
F, 19–30 y	644	3,089	1,044	1,462	1,725
Standard error		66	153	69	61
F, 31–50 y	832	3,355	1,396	1,796	2,046
Standard error		69	114	114	125
F, 51–70 y	645	3,162	1,444	1,858	2,108
Standard error		71	306	161	149
F, 71+ y	393	2,824	1,376	1,711	1,911
Standard error		48	156	136	121
P/L	97	3,681	1,497	2,090	2,427
Standard error		216	1,640	1,230	995
All individuals (non-P/L)	6,124	3,513	1,391	1,854	2,131
Standard error		36	35	31	30
All individuals (+P/L)	6,221	3,516	1,387	1,852	2,130
Standard error		36	36	34	33

[a] M = male, F = female, P/L = pregnant and/or lactating.

NOTE: Data are limited to individuals who provided a valid response to a question on usual plain drinking water intake, provided a complete and reliable 24-hour dietary recall, and provided at least one valid response to questions on participation in leisure time exercise or physical activities. Participants reported the frequency of walking, jogging or running, bicycling or using an exercise bike, swimming, aerobics or aerobic dancing, other dancing, calisthenics or exercises, garden or yard work, and lifting weights in the past month. Four open-ended questions regarding other exercises, sports or physically active hobbies (not mentioned above) were asked. Females who were pregnant, lactating, or had "blank but applicable" pregnancy or lactating status data or

25th	50th	75th	90th	95th	99th
2,734	3,348	4,097	4,912	5,475	6,714
332	165	422	838	1,150	1,910
3,123	3,783	4,574	5,419	5,995	7,245
155	95	115	242	349	614
3,060	3,767	4,647	5,623	6,305	7,824
92	82	101	167	230	401
2,773	3,421	4,238	5,154	5,799	7,244
68	83	126	203	272	454
2,535	3,048	3,667	4,331	4,785	5,773
61	58	97	194	279	498
2,123	2,740	3,469	4,230	4,735	5,794
281	245	273	467	661	1,150
2,236	2,926	3,767	4,666	5,272	6,554
76	68	95	141	169	260
2,523	3,156	3,957	4,903	5,598	7,218
118	64	150	151	254	807
2,550	3,060	3,649	4,333	4,824	5,904
190	73	200	180	303	992
2,282	2,751	3,287	3,830	4,184	4,914
90	53	77	164	231	387
3,012	3,676	4,338	4,933	5,290	5,976
585	238	509	932	1,200	1,740
2,618	3,298	4,166	5,141	5,892	7,691
29	34	49	77	102	176
2,620	3,302	4,171	5,149	5,898	7,690
34	34	49	81	104	173

who responded "I don't know" to questions on pregnancy or lactating status were excluded from the analysis. Frequency of activity per week was calculated from frequency of activity reported per month; the frequency reflects the sum of the frequencies calculated for each reported activity.

Total water intake reflects the sum of drinking water and the water content of all foods and beverages consumed.

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation (2002).

I

Dose-Response Effects of Sodium Intake on Blood Pressure

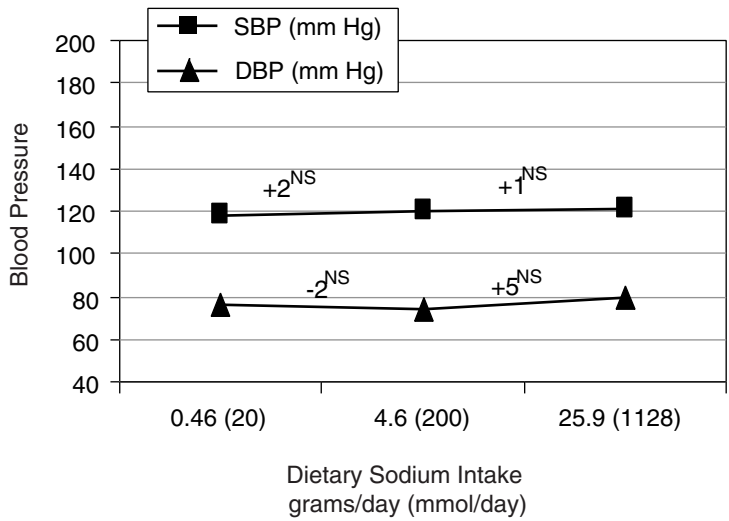

FIGURE I-1 Blood pressure (mm Hg) according to dietary sodium intake in g/d (mmol/d) among 8 normotensive men and women. Each sodium level was provided for 5 d. NS = not significantly different. Data from Roos et al. (1985).

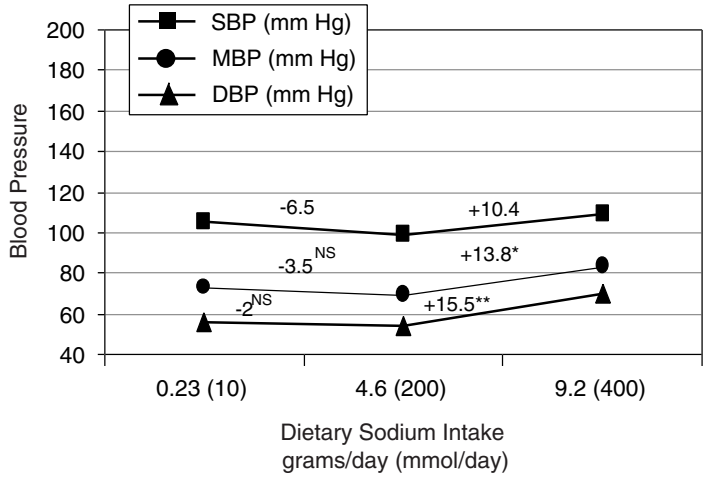

FIGURE I-2 Blood pressure (mm Hg) according to dietary sodium intake in g/d (mmol/d) among 6 normotensive subjects at risk of hypertension. Each sodium level was provided for 4 d. Systolic blood pressures were calculated from the formula mean blood pressure = 2/3 diastolic blood pressure + 1/3 systolic blood pressure. NS = not significantly different; $*p < 0.001$; $**p < 0.05$. Data from Sullivan et al. (1980).

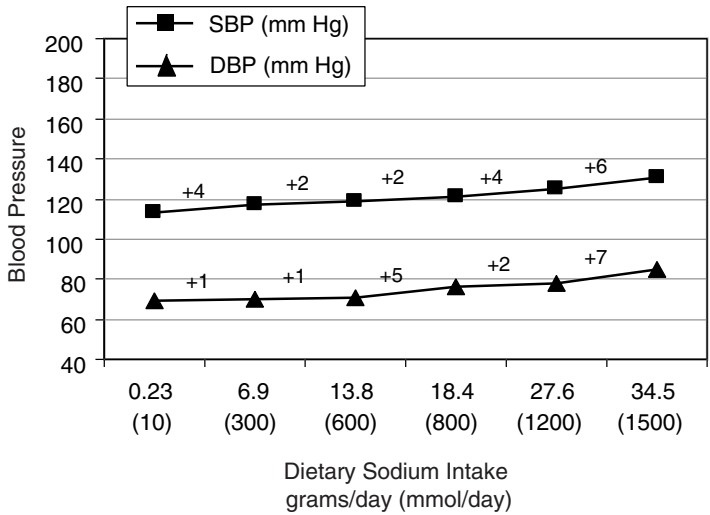

FIGURE I-3 Blood pressure (mm Hg) according to dietary sodium intake in g/d (mmol/d) among 14 normotensive men. Each sodium level was provided for 3–7 d. Significant difference between 10 and 800 mmol/d ($p < 0.05$). Data from Luft et al. (1979).

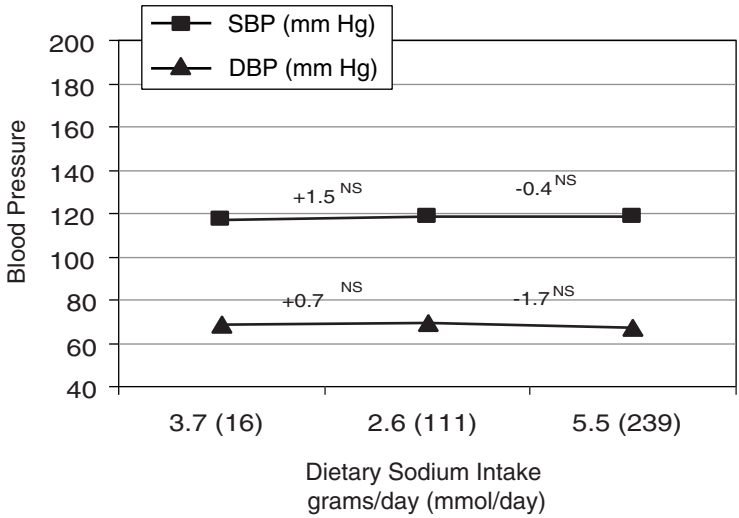

FIGURE I-4 Blood pressure (mm Hg) according to dietary sodium intake in g/d (mmol/d) among 11 normotensive men and women with a family history of hypertension. Each sodium level was provided for 9 d. NS = not significantly different. Data from Fuchs et al. (1987).

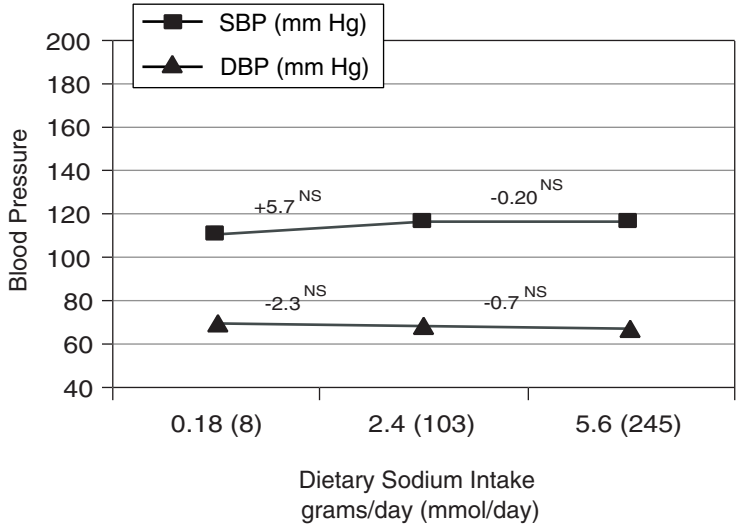

FIGURE I-5 Blood pressure (mm Hg) according to dietary sodium intake in g/d (mmol/d) among 6 normotensive men and women without family history of hypertension. Each sodium level was provided for 9 d. NS = not significantly different. Data from Fuchs et al. (1987).

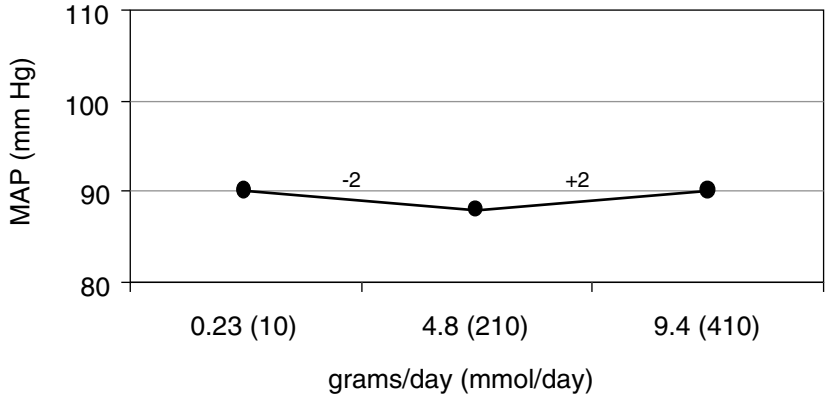

FIGURE I-6 Mean supine blood pressure (mm Hg) according to dietary sodium intake in g/d (mmol/d) among 8 normotensive men. Each sodium level was provided for 4 wk. NS = not significantly different. Data from Kirkendall et al. (1976).

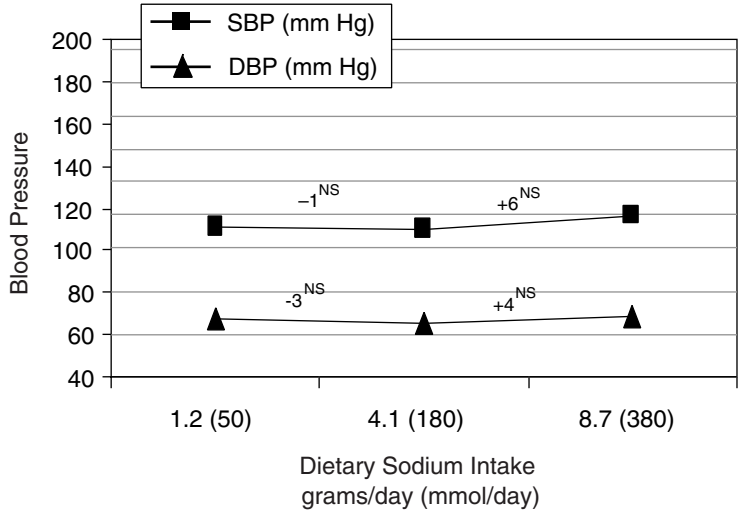

FIGURE I-7 Blood pressure (mm Hg) according to dietary sodium intake in g/d (mmol/d) among 10 normotensive men and women. Each sodium level was provided for 4 d. NS = not significantly different. Data from Bruun et al. (1990).

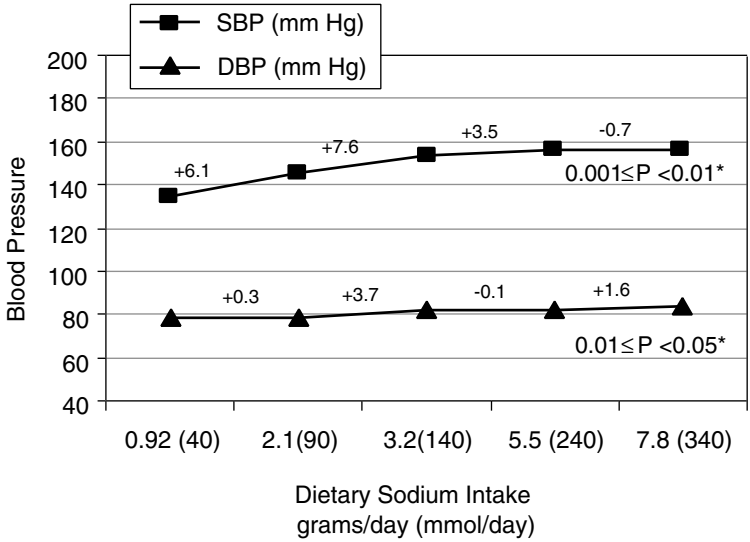

FIGURE I-8 Blood pressure (mm Hg) according to sodium intake in g/d (mmol/d) among 17 normotensive elderly subjects. Each sodium level was provided for 2 wk. *P-ANOVA simultaneously comparing the four pair-wise blood pressure differences between the lowest sodium level (baseline) and each of the four higher sodium levels. Data from Johnson et al. (2001).

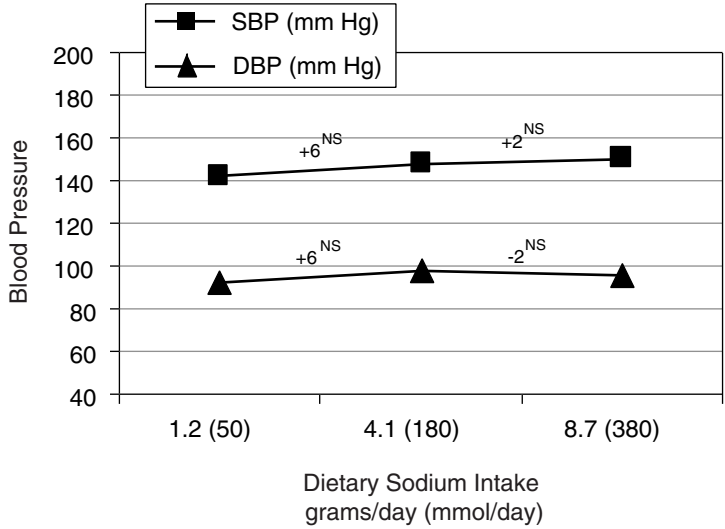

FIGURE I-9 Blood pressure (mm Hg) according to dietary sodium intake in g/d (mmol/d) among 12 hypertensive men and women. Each sodium level was provided for 4 d. NS = not significantly different. Data from Bruun et al. (1990).

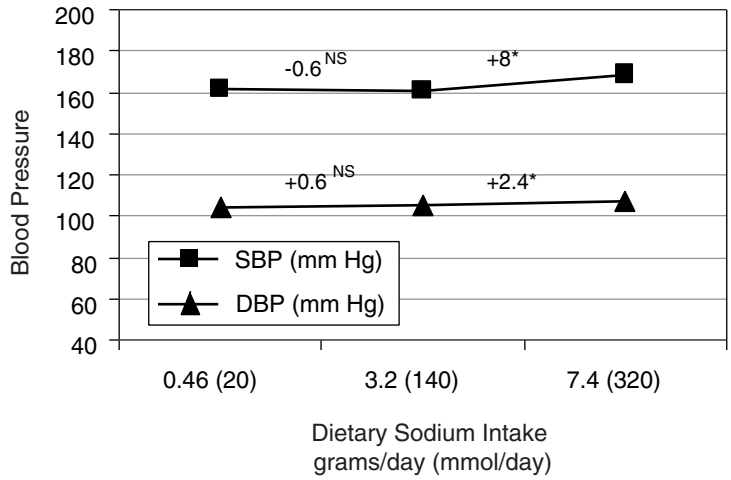

FIGURE I-10 Blood pressure (mm Hg) according to dietary sodium intake in g/d (mmol/d) among 61 hypertensive men. Each sodium level was provided for 2 wk. NS = not significantly different; *$p < 0.05$. Data from Ferri et al. (1996).

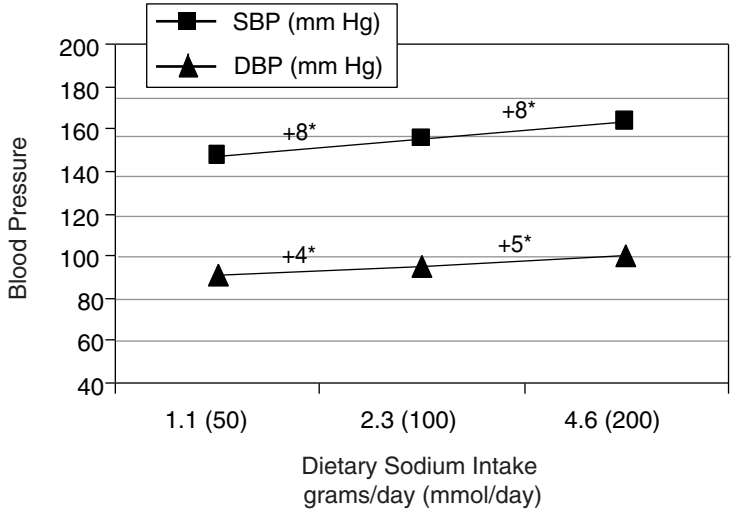

FIGURE I-11 Blood pressure (mm Hg) according to dietary sodium intake in g/d (mmol/d) among 20 hypertensive men and women. Each sodium level was provided for 4 wk. *$p < 0.01$. Data from MacGregor et al. (1989).

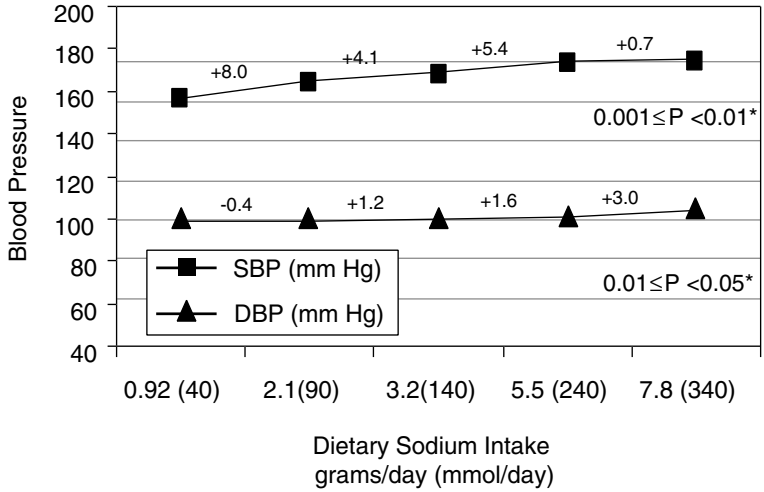

FIGURE I-12 Blood pressure (mm Hg) according to sodium intake in g/d (mmol/d) among 8 systolic diastolic hypertensive elderly subjects. Each sodium level was provided for 2 wk. *P-ANOVA simultaneously comparing the four pair-wise blood pressure differences between the lowest sodium level (baseline) and each of the four higher sodium levels. Data from Johnson et al. (2001).

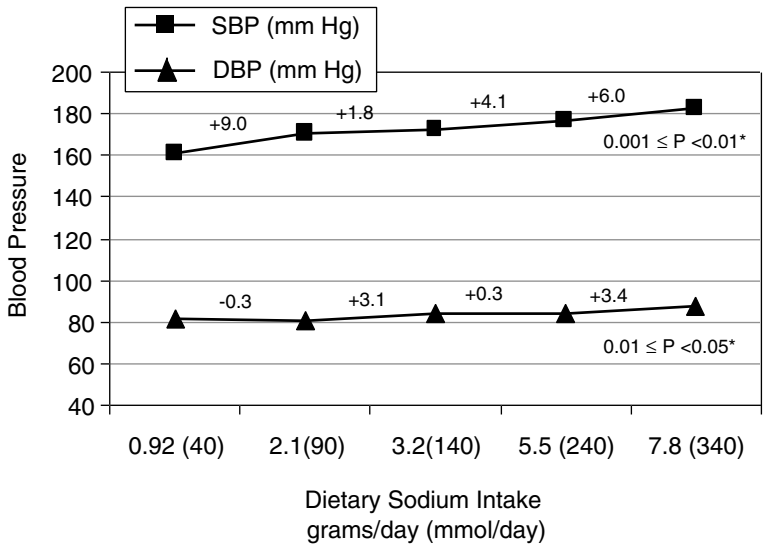

FIGURE I-13 Blood pressure (mm Hg) according to sodium dose in g/d (mmol/d) among 15 isolated systolic hypertensive elderly subjects. Each sodium dose was provided for 2 wk. *P-ANOVA simultaneously comparing the four pair-wise blood pressure differences between the lowest sodium level (baseline) and each of the four higher sodium levels. Data from Johnson et al. (2001).

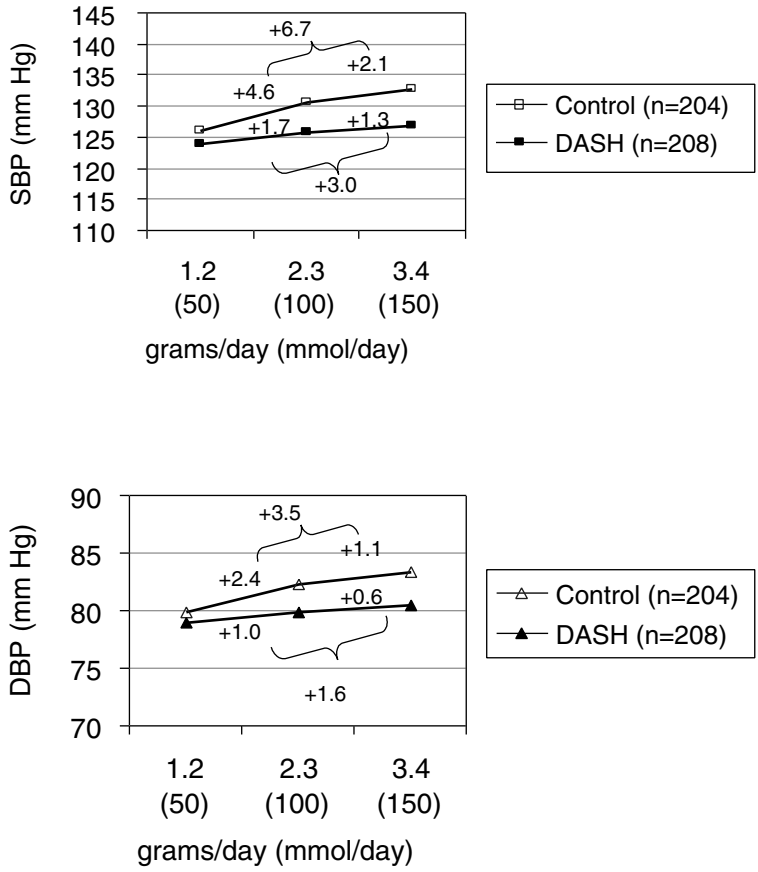

FIGURE I-14 Analyses from the Dietary Approaches to Stop Hypertension (DASH)-Sodium Trial: Effect of sodium level on systolic and diastolic blood pressure in 412 normotensives and hypertensive participants. Sodium levels defined as higher = 3.5 g/d/2,000 kcal (150 mmol/d), intermediate = 2.3 g/d/2,000 kcal (100 mmol/d), and lower = 1.2 g/d/2,000 kcal (50 mmol/d). Adapted with permission from Sacks et al. (2001). Copyright 2001 by the Massachusetts Medical Society.

TABLE I-1a Mean Blood Pressure by Diet and by Sodium Level, Dietary Approaches to Stop Hypertension (DASH)-Sodium Trial

	Systolic			Diastolic		
Diet	Higher	Intermediate	Lower	Higher	Intermediate	Lower
Control diet (n = 204)	132.8	130.7	126.1	83.4	82.3	79.9
DASH diet (n = 208)	126.9	125.6	123.9	80.5	79.9	78.9

SOURCE: Sacks et al. (2001).

TABLE I-1b Effect of Decreased Sodium on Systolic and Diastolic Blood Pressure, Control Diet (n = 204) in DASH-Sodium Trial

	Systolic			Diastolic		
	Mean Change	Standard Error	P-value	Mean Change	Standard Error	P-value
Higher to lower	–6.7	0.58	< 0.0001	–3.5	0.38	< 0.0001
Higher to intermediate	–2.1	0.58	0.0003	–1.1	0.38	0.0044
Intermediate to lower	–4.6	0.60	< 0.0001	–2.4	0.39	< 0.0001

SOURCE: Sacks et al. (2001).

TABLE I-1c Effect of Decreased Sodium on Systolic and Diastolic Blood Pressure, DASH Diet (n = 208), in DASH-Sodium Trial

	Systolic			Diastolic		
	Mean Change	Standard Error	*P*-value	Mean Change	Standard Error	*P*-value
Higher to lower	–3.0	0.58	< 0.0001	–1.6	0.37	< 0.0001
Higher to intermediate	–1.3	0.58	0.03	–0.6	0.37	0.09
Intermediate to lower	–1.7	0.59	0.003	–1.0	0.38	0.01

SOURCE: Sacks et al. (2001).

TABLE I-2 Design Features of Dose-Response Trials that Tested the Effects of Sodium Intake on Blood Pressure

Study	Figure (Appendix I)	Reference	*N*
Nonhypertensive			
1	1	Roos et al. (1985)	8
2	2	Sullivan et al. (1980)	6
3	3	Luft et al. (1979)	14
4	4	Fuchs et al. (1987), at risk of hypertension	17
	5	Fuchs et al. (1987), not at risk of hypertension	17
5	6	Kirkendall et al. (1976)	8
6	7	Bruun et al. (1990)	10
7	8	Johnson et al. (2001)	17
Hypertensive			
	9	Bruun et al. (1990)	12
8	10	Ferri et al. (1996)	61
9	11	MacGregor et al. (1989)	20
	12	Johnson et al. (2001), systolic-diastolic hypertension	8
	13	Johnson et al. (2001), isolated systolic hypertension	15
Both nonhypertensive and hypertensive			
10	14	Sacks et al. (2001) DASH[c] diet	208
		Control diet	204

[a] Urinary sodium.
[b] Urinary potassium.
[c] DASH = Dietary Approaches to Stop Hypertension.

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Ferri C, Bellini C, Carlomagno A, Desideri G, Santucci A. 1996. Active kallikrein response to changes in sodium-chloride intake in essential hypertensive patients. *J Am Soc Nephrol* 7:443–453.

Fuchs FD, Wannmacher CM, Wannmacher L, Guimaraes FS, Rosito GA, Gastaldo G, Hoeffel CP, Wagner EM. 1987. Effect of sodium intake on blood pressure, serum levels and renal excretion of sodium and potassium in normotensives with and without familial predisposition to hypertension. *Braz J Med Biol Res* 20:25–34.

Johnson AG, Nguyen TV, Davis D. 2001. Blood pressure is linked to salt intake and modulated by the angiotensinogen gene in normotensive and hypertensive elderly subjects. *J Hypertens* 19:1053–1060.

Kirkendall WM, Conner EW, Abboud F, Rastogi SP, Anderson TA, Fry M. 1976. The effect of dietary sodium chloride on blood pressure, body fluids, electro-

Duration (days)	Feeding Study	Design	Range of Sodium g/d (mmol/d)		Potassium Level g/d (mmol/d)
			Lowest	Highest	
5	Yes	Dose-escalation	0.46 (20)	25.9 (1,128)	3.1 (80)
4	Yes	Crossover	0.23 (10)	9.2 (400)	2.3 (60)
3–7	Yes	Dose-escalation	0.23 (10)	34.5 (1,500)	3.1 (80)
9	No	Crossover	3.7 (16)[a]	5.5 (239)[a]	≈ 1.9 (50)[b]
9	No	Crossover	0.18 (8)[a]	5.6 (245)[a]	≈ 1.9 (50)[b]
28	Yes	Crossover	0.23 (10)	9.4 (410)	3.9 (100)
4	Yes	Crossover	1.2 (50)	8.7 (380)	3.1 (80)
14	Yes	Crossover	0.92 (40)	7.8 (340)	≈ 1.2 (30)[b]
4	Yes	Crossover	1.2 (50)	8.7 (380)	3.1 (80)
14	Yes	Crossover	0.46 (20)	7.4 (320)	2.7 (70)
28	No	Crossover	1.2 (50)	4.6 (200)	2.7 (70)
14	Yes	Crossover	0.92 (40)	7.8 (340)	≈ 1.2 (30)[b]
14	Yes	Crossover	0.92 (40)	7.8 (340)	≈ 1.2 (30)[b]
28	Yes	Crossover	1.5 (67)[a]	3.3 (144)	3.1 (79)[b]
28	Yes	Crossover	1.5 (64)[a]	3.2 (141)[a]	1.6 (41)[b]

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J

U.S. Serum Electrolyte Concentration Data from the Third National Health and Nutrition Examination Survey, 1988–1994

TABLE J-1 Mean and Selected Percentiles of Serum Potassium (mmol/L): United States, NHANES III, 1988–1994

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
M, 14–18 y	1,196	4.18	3.82	3.92	3.97
Standard error		0.02	0.07	0.05	0.05
M, 19–50 y	4,277	4.08	3.63	3.76	3.83
Standard error		0.01	0.02	0.02	0.02
M, 51–70 y	1,953	4.11	3.43	3.65	3.76
Standard error		0.01	0.03	0.02	0.02
M, 71+ y	1,328	4.26	3.60	3.80	3.91
Standard error		0.02	0.04	0.03	0.02
F, 14–18 y	1,269	4.06	3.69	3.79	3.84
Standard error		0.02	0.04	0.03	0.03
F, 19–50 y	4,675	4.00	3.52	3.67	3.74
Standard error		0.01	0.03	0.02	0.02
F, 51–70 y	2,046	4.04	3.38	3.60	3.71
Standard error		0.01	0.03	0.03	0.02
F, 71+ y	1,489	4.11	3.34	3.58	3.70
Standard error		0.02	0.03	0.02	0.02
Pregnant	323	3.91	3.52	3.62	3.68
Standard error		0.02	0.18	0.14	0.11
Lactating	100	4.08	3.61	3.76	3.84
Standard error		0.05	0.37	0.25	0.19

[a] M = male, F = female (not pregnant and/or lactating).

NOTE: Data were adjusted using the Iowa State University method to provide estimates of usual serum potassium concentrations. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Females who had "blank but applicable" pregnancy or lactating status data or who responded "I don't know" to questions on pregnancy or lactating status were excluded from the analysis.

25th	50th	75th	90th	95th	99th
4.07	4.18	4.29	4.40	4.47	4.59
0.03	0.02	0.03	0.05	0.06	0.09
3.94	4.07	4.21	4.34	4.42	4.58
0.01	0.01	0.01	0.02	0.02	0.03
3.94	4.12	4.29	4.46	4.56	4.77
0.02	0.02	0.02	0.02	0.02	0.02
4.07	4.25	4.43	4.62	4.74	5.00
0.02	0.02	0.02	0.03	0.03	0.05
3.94	4.05	4.17	4.28	4.35	4.48
0.02	0.02	0.02	0.03	0.04	0.06
3.86	3.99	4.13	4.26	4.35	4.53
0.01	0.01	0.01	0.02	0.02	0.03
3.87	4.04	4.20	4.37	4.47	4.69
0.02	0.01	0.01	0.02	0.02	0.03
3.90	4.10	4.32	4.54	4.69	5.01
0.01	0.02	0.02	0.03	0.04	0.06
3.78	3.90	4.03	4.16	4.24	4.40
0.07	0.03	0.06	0.12	0.16	0.24
3.96	4.09	4.21	4.31	4.37	4.47
0.10	0.06	0.11	0.17	0.21	0.27

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics (2003).

TABLE J-2 Mean and Selected Percentiles of Serum Sodium (mmol/L): United States, NHANES III, 1988–1994

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
M, 14–18 y	1,196	141.4	138.6	139.5	139.9
Standard error		0.1	0.2	0.2	0.1
M, 19–50 y	4,277	141.7	138.7	139.7	140.1
Standard error		0.1	0.2	0.2	0.1
M, 51–70 y	1,953	141.5	137.9	139.1	139.7
Standard error		0.1	0.2	0.2	0.2
M, 71+ y	1,328	141.6	137.9	139.1	139.7
Standard error		0.1	0.2	0.2	0.2
F, 14–18 y	1,269	140.8	136.4	138.3	138.9
Standard error		1.3	8.8	3.4	2.3
F, 19–50 y	4,675	140.9	137.5	138.4	139.0
Standard error		0.1	0.2	0.2	0.1
F, 51–70 y	2,046	141.5	136.4	138.3	139.1
Standard error		0.1	0.6	0.3	0.3
F, 71+ y	1,489	141.3	135.6	137.7	138.6
Standard error		0.2	0.4	0.3	0.3
Pregnant	323	138.8	134.5	136.3	137.0
Standard error		0.2	0.8	0.5	0.4
Lactating	100	141.9	139.3	140.2	140.6
Standard error		0.3	0.5	0.3	0.3

[a] M = male, F = female (not pregnant and/or lactating).

NOTE: Data were adjusted using the Iowa State University method to provide estimates of usual serum potassium concentrations. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Females who had "blank but applicable" pregnancy or lactating status data or who responded "I don't know" to questions on pregnancy or lactating status were excluded from the analysis.

25th	50th	75th	90th	95th	99th
140.6	141.4	142.1	142.8	143.3	144.3
0.1	0.1	0.1	0.1	0.2	0.3
140.9	141.7	142.5	143.3	143.7	144.7
0.1	0.1	0.1	0.1	0.1	0.1
140.6	141.5	142.5	143.3	143.8	144.7
0.1	0.1	0.1	0.1	0.1	0.2
140.7	141.6	142.6	143.4	144.0	145.0
0.1	0.1	0.1	0.1	0.1	0.2
139.9	140.8	141.8	142.5	143.0	144.0
1.6	1.1	0.4	0.2	0.2	0.3
139.9	140.8	141.8	142.7	143.4	144.5
0.1	0.1	0.1	0.1	0.1	0.3
140.3	141.5	142.7	143.8	144.4	145.7
0.2	0.1	0.2	0.2	0.2	0.3
140.1	141.4	142.6	143.8	144.6	146.2
0.2	0.2	0.2	0.2	0.3	0.5
137.9	138.7	139.8	140.9	141.5	142.7
0.2	0.2	0.2	0.3	0.4	0.4
141.3	142.0	142.6	143.2	143.5	144.0
0.3	0.3	0.3	0.2	0.2	0.3

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics (2003).

TABLE J-3 Mean and Selected Percentiles of Serum Chloride (mmol/L): United States, NHANES III, 1988–1994

			Percentile		
Sex/Age Category[a]	*n*	Mean	1st	5th	10th
M, 14–18 y	1,196	104.1	100.4	101.5	102.1
Standard error		0.2	0.6	0.5	0.4
M, 19–50 y	4,277	104.5	99.9	101.3	102.0
Standard error		0.2	0.3	0.3	0.3
M, 51–70 y	1,953	104.3	97.4	99.8	101.0
Standard error		0.2	0.5	0.6	0.5
M, 71+ y	1,328	104.1	97.3	99.6	100.8
Standard error		0.2	0.8	0.4	0.3
F, 14–18 y	1,269	104.8	100.4	101.7	102.4
Standard error		0.2	0.6	0.4	0.3
F, 19–50 y	4,675	105.0	100.0	101.5	102.4
Standard error		0.2	0.4	0.3	0.3
F, 51–70 y	2,046	104.1	97.0	99.4	100.6
Standard error		0.2	0.5	0.4	0.4
F, 71+ y	1,489	103.7	95.9	98.7	100.0
Standard error		0.2	1.0	0.5	0.4
Pregnant	323	105.1	100.8	102.2	102.9
Standard error		0.4	1.9	1.3	1.0
Lactating	100	105.3	101.2	102.5	103.2
Standard error		0.5	2.8	1.8	1.4

[a] M = male, F = female (not pregnant and/or lactating).

NOTE: Data were adjusted using the Iowa State University method to provide estimates of usual serum potassium concentrations. Means, standard errors, and percentiles were obtained using C-Side. Standard errors were estimated via jackknife replication. Each standard error has 49 degrees of freedom. Females who had "blank but applicable" pregnancy or lactating status data or who responded "I don't know" to questions on pregnancy or lactating status were excluded from the analysis.

25th	50th	75th	90th	95th	99th
103.0	104.1	105.1	106.0	106.6	107.6
0.3	0.2	0.2	0.3	0.4	0.5
103.2	104.5	105.8	106.9	107.6	108.9
0.3	0.2	0.2	0.2	0.2	0.4
102.7	104.4	106.0	107.4	108.3	109.9
0.3	0.3	0.3	0.2	0.3	0.4
102.5	104.2	105.8	107.3	108.2	109.9
0.2	0.2	0.2	0.3	0.4	0.8
103.6	104.8	106.0	107.1	107.7	108.8
0.3	0.2	0.3	0.3	0.3	0.4
103.7	105.1	106.5	107.6	108.3	109.5
0.3	0.2	0.2	0.2	0.2	0.4
102.4	104.2	105.9	107.5	108.4	110.1
0.2	0.3	0.3	0.3	0.3	0.4
102.0	103.8	105.6	107.1	108.0	109.6
0.3	0.3	0.2	0.3	0.4	0.5
104.0	105.1	106.2	107.2	107.9	109.1
0.6	0.4	0.6	0.9	1.2	1.7
104.3	105.4	106.4	107.2	107.6	108.4
0.8	0.5	0.7	1.0	1.3	1.8

DATA SOURCE: U.S. Department of Health and Human Services, National Center for Health Statistics, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

SOURCE: ENVIRON International Corporation and Iowa State University Department of Statistics (2003).

K

Options for Dealing with Uncertainties

Methods for dealing with uncertainties in scientific data are generally understood by working scientists and require no special discussion here except to point out that such uncertainties should be explicitly acknowledged and taken into account whenever a risk assessment is undertaken. More subtle and difficult problems are created by uncertainties associated with some of the inferences that must be made in the absence of directly applicable data; much confusion and inconsistency can result if they are not recognized and dealt with in advance of undertaking a risk assessment.

The most significant inference uncertainties arise in risk assessments whenever attempts are made to answer the following questions (NRC, 1994):

- What set or sets of hazard and dose-response data (for a given substance) should be used to characterize risk in the population of interest?
- If animal data are to be used for risk characterization, which endpoints for adverse effects should be considered?
- If animal data are to be used for risk characterization, what measure of dose (e.g., dose per unit body weight, body surface, or dietary intake) should be used for scaling between animals and humans?
- What is the expected variability in dose-response between animals and humans?
- If human data are to be used for risk characterization, which adverse effects should be used?

- What is the expected variability in dose-response among members of the human population?
- How should data from subchronic exposure studies be used to estimate chronic effects?
- How should problems of differences in route of exposure within and between species be dealt with?
- How should the threshold dose be estimated for the human population?
- If a threshold in the dose-response relationship seems unlikely, how should a low-dose risk be modeled?
- What model should be chosen to represent the distribution of exposures in the population of interest when data relating to exposures are limited?
- When interspecies extrapolations are required, what should be assumed about relative rates of absorption from the gastrointestinal tracts of animals and of humans?
- For which percentiles on the distribution of population exposures should risks be characterized?

At least partial, empirically based answers to some of these questions may be available for some of the nutrients under review, but in no case is scientific information likely to be sufficient to provide a highly certain answer; in many cases there will be no relevant data for the nutrient in question.

It should be recognized that for several of these questions, certain inferences have been widespread for long periods of time; thus it may seem unnecessary to raise these uncertainties anew. When several sets of animal toxicology data are available, for example, and data are not sufficient for identifying the set (i.e., species, strain, and adverse effects endpoint) that best predicts human response, it has become traditional to select that set for which toxic responses occur at the lowest dose (the most sensitive set). In the absence of definitive empirical data applicable to a specific case, it is generally assumed that there will not be more than a tenfold variation in response among members of the human population. In the absence of absorption data, it is generally assumed that humans will absorb the chemical at the same rate as the animal species used to model human risk. In the absence of complete understanding of biological mechanisms, it is generally assumed that, except possibly for certain carcinogens, a threshold dose must be exceeded before toxicity is expressed. These types of long-standing assumptions, which are necessary to complete a risk assessment, are recognized by risk assessors as attempts to deal with uncertainties (NRC, 1994).

A past National Research Council (NRC) report (1983) recommended adoption of the concepts and definitions that have been discussed in this report. The NRC committee recognized that throughout a risk assessment, data and basic knowledge will be lacking and risk assessors will be faced with several scientifically plausible options (called inference options by the NRC) for dealing with questions such as those presented above. For example, several scientifically supportable options for dose scaling across species and for high- to low-dose extrapolation will exist, but there will be no ready means to identify those that are clearly best supported. The NRC committee recommended that regulatory agencies in the United States identify the needed inference options in risk assessment and specify, through written risk assessment guidelines, the specific options that will be used for all assessments. Agencies in the United States have identified the specific models to be used to fill gaps in data and knowledge; these have come to be called *default options* (EPA, 1986).

The use of defaults to fill knowledge and data gaps in risk assessment has the advantage of ensuring consistency in approach (the same defaults are used for each assessment) and minimizing or eliminating case-by-case manipulations of the conduct of risk assessment to meet predetermined risk management objectives. The major disadvantage of the use of defaults is the potential for displacement of scientific judgment by excessively rigid guidelines. A remedy for this disadvantage was also suggested by the NRC committee: Risk assessors should be allowed to replace defaults with alternative factors in specific cases of chemicals for which relevant scientific data are available to support alternatives. The risk assessors' obligation in such cases is to provide explicit justification for any such departure. Guidelines for risk assessment issued by the U.S. Environmental Protection Agency (EPA, 1986), for example, specifically allow for such departures.

The use of preselected defaults is not the only way to deal with model uncertainties. Another option is to allow risk assessors complete freedom to pursue whatever approaches they judge applicable in specific cases. Because many of the uncertainties cannot be resolved scientifically, case-by-case judgments without some guidance on how to deal with them will lead to difficulties in achieving scientific consensus, and the results of the assessment may not be credible.

Another option for dealing with uncertainties is to allow risk assessors to develop a range of estimates based on application of both defaults and alternative inferences that, in specific cases, have some

degree of scientific support. Indeed, appropriate analysis of uncertainties seems to require such a presentation of risk results. Although presenting a number of plausible risk estimates has the advantage that it would seem to more faithfully reflect the true state of scientific understanding, there are no well-established criteria for using such complex results in risk management.

The various approaches to dealing with uncertainties inherent in risk assessment are summarized in Table K-1.

As can be seen in the nutrient chapters (IOM, 2002/2005), specific default assumptions for assessing nutrient risks have not been recommended. Rather, the approach calls for case-by-case judgments, with the recommendation that the basis for the choices made be explicitly stated. Some general guidelines for making these choices are, however, offered.

TABLE K-1 Approaches for Dealing with Uncertainties in a Risk Assessment Program

Program Model	Advantages	Disadvantages
Case-by-case judgments by experts	Flexibility; high potential to maximize use of most relevant scientific information bearing on specific issues	Potential for inconsistent treatment of different issues; difficulty in achieving consensus; need to agree on defaults
Written guidelines specifying defaults for data and model uncertainties (with allowance for departures in specific cases)	Consistent treatment of different issues; maximization of transparency of process; resolution of scientific disagreements possible by resorting to defaults	Possible difficulty in justifying departure or achieving consensus among scientists that departures are justified in specific cases; danger that uncertainties will be overlooked
Presentation of full array of estimates from all scientifically plausible models by assessors	Maximization of use of scientific information; reasonably reliable portrayal of true state of scientific understanding	Highly complex characterization of risk, with no easy way to discriminate among estimates; size of required effort may not be commensurate with utility of the outcome

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L
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American Dietetic Association
American Heart Association
American Society for Clinical Nutrition
American Society for Nutritional Sciences

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M

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DAVID H. BAKER, Ph.D., is a professor of nutrition at the University of Illinois, Urbana-Champaign. He received his Ph.D. in nutrition from the University of Illinois. He has published over 450 peer-reviewed articles on the metabolism and requirements of various nutrients, including sulfur amino acids and sulfate. He is a member

of the American Society for Nutritional Sciences (ASNS), the American Society of Animal Science, and the Poultry Science Association. He has served on the editorial boards for the *Journal of Nutrition, Journal of Animal Science, Poultry Science*, and *Nutrition Reviews*. Dr. Baker served on the National Research Council's Board on Agriculture and Natural Resources (BANR) as well as on BANR's Subcommittees on Swine Nutrition, Bioavailability of Nutrients, and Cat Nutrition. He was named a University Scholar at Illinois in 1986, and has received numerous research awards, including the ASNS Borden Award and the Dannon Mentoring Award. He is currently completing a 4-year term on the Board of Directors of the Federation of American Societies for Experimental Biology (FASEB).

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MYRON H. WEINBERGER, M.D., is a professor of medicine and director of the Hypertension Research Center at the Indiana University School of Medicine. He received his M.D. from the Indiana University School of Medicine and specializes in internal medicine and hypertension. In addition to serving on numerous scientific review committees, Dr. Weinberger is a member of several editorial boards, including those of *Hypertension* and *Journal of the American College of Nutrition*. He has published over 200 scientific articles on hypertension, many of which relate to the roles of sodium and/or potassium. Dr. Weinberger received the Robert Tigerstedt Award from the American Society of Hypertension and the Page-Bradley Lifetime Achievement Award from the Council for High Blood Pressure Research of the American Heart Association for his research in hypertension.

PAUL K. WHELTON, M.D., M.Sc., is Senior Vice President for Health Sciences at Tulane University and a professor both of epidemiology at the Tulane University School of Public Health and Tropical Medicine and of medicine at the Tulane University School of Medicine. He was previously dean of the School of Public Health and Tropical Medicine and of the School of Medicine, both at Tulane University. Prior to that, he was director of the Welch Center for Prevention, Epidemiology and Clinical Research; the Johns Hopkins Outpatient Clinical Research Center; and the Program in

Clinical Epidemiology at Johns Hopkins University. He earned his M.D. from the National University of Ireland and a master's in epidemiology from the University of London School of Hygiene and Tropical Medicine. He is an internationally recognized expert in the epidemiology, prevention, and treatment of cardiovascular and renal diseases. He has conducted a series of major research studies on hypertension prevention and management. Dr. Whelton has served as a consultant to many national and international health agencies and governments.

Index

A

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

R

S

T

U

V

W

Y

Z

Summary Tables, Dietary Reference Intakes

Dietary Reference Intakes (DRIs): Recommended Intakes for Individuals, Vitamins
Food and Nutrition Board, Institute of Medicine, National Academies

Life Stage Group	Vitamin A (μg/d) [a]	Vitamin C (mg/d)	Vitamin D (μg/d) [b,c]	Vitamin E (mg/d) [d]	Vitamin K (μg/d)	Thiamin (mg/d)
Infants						
0–6 mo	400*	40*	5*	4*	2.0*	0.2*
7–12 mo	500*	50*	5*	5*	2.5*	0.3*
Children						
1–3 y	**300**	**15**	5*	**6**	30*	**0.5**
4–8 y	**400**	**25**	5*	**7**	55*	**0.6**
Males						
9–13 y	**600**	**45**	5*	**11**	60*	**0.9**
14–18 y	**900**	**75**	5*	**15**	75*	**1.2**
19–30 y	**900**	**90**	5*	**15**	120*	**1.2**
31–50 y	**900**	**90**	5*	**15**	120*	**1.2**
51–70 y	**900**	**90**	10*	**15**	120*	**1.2**
> 70 y	**900**	**90**	15*	**15**	120*	**1.2**
Females						
9–13 y	**600**	**45**	5*	**11**	60*	**0.9**
14–18 y	**700**	**65**	5*	**15**	75*	**1.0**
19–30 y	**700**	**75**	5*	**15**	90*	**1.1**
31–50 y	**700**	**75**	5*	**15**	90*	**1.1**
51–70 y	**700**	**75**	10*	**15**	90*	**1.1**
> 70 y	**700**	**75**	15*	**15**	90*	**1.1**
Pregnancy						
14–18 y	**750**	**80**	5*	**15**	75*	**1.4**
19–30 y	**770**	**85**	5*	**15**	90*	**1.4**
31–50 y	**770**	**85**	5*	**15**	90*	**1.4**
Lactation						
14–18 y	**1,200**	**115**	5*	**19**	75*	**1.4**
19–30 y	**1,300**	**120**	5*	**19**	90*	**1.4**
31–50 y	**1,300**	**120**	5*	**19**	90*	**1.4**

NOTE: This table (taken from the DRI reports, see www.nap.edu) presents Recommended Dietary Allowances (RDAs) in **bold type** and Adequate Intakes (AIs) in ordinary type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover needs of all individuals in the group, but lack of data or uncertainty in the data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a] As retinol activity equivalents (RAEs). 1 RAE = 1 μg retinol, 12 μg β-carotene, 24 μg α-carotene, or 24 μg β-cryptoxanthin. The RAE for dietary provitamin A carotenoids is twofold greater than retinol equivalents (RE), whereas the RAE for preformed vitamin A is the same as RE.

[b] As cholecalciferol. 1 μg cholecalciferol = 40 IU vitamin D.

[c] In the absence of adequate exposure to sunlight.

[d] As α-tocopherol. α-Tocopherol includes *RRR*-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the *2R*-stereoisomeric forms of α-tocopherol (*RRR*-, *RSR*-, *RRS*-, and *RSS*-α-tocopherol) that occur in fortified foods and supplements. It does not include the *2S*-stereoisomeric forms of α-tocopherol (*SRR*-, *SSR*-, *SRS*-, and *SSS*-α-tocopherol), also found in fortified foods and supplements.

[e] As niacin equivalents (NE). 1 mg of niacin = 60 mg of tryptophan; 0–6 months = preformed niacin (not NE).

[f] As dietary folate equivalents (DFE). 1 DFE = 1 μg food folate = 0.6 μg of folic acid

Riboflavin (mg/d)	Niacin (mg/d)[e]	Vitamin B_6 (mg/d)	Folate (μg/d)[f]	Vitamin B_{12} (μg/d)	Pantothenic Acid (mg/d)	Biotin (μg/d)	Choline (mg/d)[g]
0.3*	2*	0.1*	65*	0.4*	1.7*	5*	125*
0.4*	4*	0.3*	80*	0.5*	1.8*	6*	150*
0.5	**6**	**0.5**	**150**	**0.9**	2*	8*	200*
0.6	**8**	**0.6**	**200**	**1.2**	3*	12*	250*
0.9	**12**	**1.0**	**300**	**1.8**	4*	20*	375*
1.3	**16**	**1.3**	**400**	**2.4**	5*	25*	550*
1.3	**16**	**1.3**	**400**	**2.4**	5*	30*	550*
1.3	**16**	**1.3**	**400**	**2.4**	5*	30*	550*
1.3	**16**	**1.7**	**400**	**2.4**[h]	5*	30*	550*
1.3	**16**	**1.7**	**400**	**2.4**[h]	5*	30*	550*
0.9	**12**	**1.0**	**300**	**1.8**	4*	20*	375*
1.0	**14**	**1.2**	**400**[i]	**2.4**	5*	25*	400*
1.1	**14**	**1.3**	**400**[i]	**2.4**	5*	30*	425*
1.1	**14**	**1.3**	**400**[i]	**2.4**	5*	30*	425*
1.1	**14**	**1.5**	**400**	**2.4**[h]	5*	30*	425*
1.1	**14**	**1.5**	**400**	**2.4**[h]	5*	30*	425*
1.4	**18**	**1.9**	**600**[j]	**2.6**	6*	30*	450*
1.4	**18**	**1.9**	**600**[j]	**2.6**	6*	30*	450*
1.4	**18**	**1.9**	**600**[j]	**2.6**	6*	30*	450*
1.6	**17**	**2.0**	**500**	**2.8**	7*	35*	550*
1.6	**17**	**2.0**	**500**	**2.8**	7*	35*	550*
1.6	**17**	**2.0**	**500**	**2.8**	7*	35*	550*

from fortified food or as a supplement consumed with food = 0.5 μg of a supplement taken on an empty stomach.

[g] Although AIs have been set for choline, there are few data to assess whether a dietary supply of choline is needed at all stages of the life cycle, and it may be that the choline requirement can be met by endogenous synthesis at some of these stages.

[h] Because 10 to 30 percent of older people may malabsorb food-bound B_{12}, it is advisable for those older than 50 years to meet their RDA mainly by consuming foods fortified with B_{12} or a supplement containing B_{12}.

[i] In view of evidence linking folate intake with neural tube defects in the fetus, it is recommended that all women capable of becoming pregnant consume 400 μg from supplements or fortified foods in addition to intake of food folate from a varied diet.

[j] It is assumed that women will continue consuming 400 μg from supplements or fortified food until their pregnancy is confirmed and they enter prenatal care, which ordinarily occurs after the end of the periconceptional period—the critical time for formation of the neural tube.

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001); *and Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (2005). These reports may be accessed via http://www.nap.edu.

Dietary Reference Intakes (DRIs): Recommended Intakes for Individuals, Elements
Food and Nutrition Board, Institute of Medicine, National Academies

Life Stage Group	Calcium (mg/d)	Chromium (µg/d)	Copper (µg/d)	Fluoride (mg/d)	Iodine (µg/d)	Iron (mg/d)	Magnesium (mg/d)
Infants							
0–6 mo	210*	0.2*	200*	0.01*	110*	0.27*	30*
7–12 mo	270*	5.5*	220*	0.5*	130*	**11**	75*
Children							
1–3 y	500*	11*	**340**	0.7*	**90**	**7**	**80**
4–8 y	800*	15*	**440**	1*	**90**	**10**	**130**
Males							
9–13 y	1,300*	25*	**700**	2*	**120**	**8**	**240**
14–18 y	1,300*	35*	**890**	3*	**150**	**11**	**410**
19–30 y	1,000*	35*	**900**	4*	**150**	**8**	**400**
31–50 y	1,000*	35*	**900**	4*	**150**	**8**	**420**
51–70 y	1,200*	30*	**900**	4*	**150**	**8**	**420**
> 70 y	1,200*	30*	**900**	4*	**150**	**8**	**420**
Females							
9–13 y	1,300*	21*	**700**	2*	**120**	**8**	**240**
14–18 y	1,300*	24*	**890**	3*	**150**	**15**	**360**
19–30 y	1,000*	25*	**900**	3*	**150**	**18**	**310**
31–50 y	1,000*	25*	**900**	3*	**150**	**18**	**320**
51–70 y	1,200*	20*	**900**	3*	**150**	**8**	**320**
> 70 y	1,200*	20*	**900**	3*	**150**	**8**	**320**
Pregnancy							
14–18 y	1,300*	29*	**1,000**	3*	**220**	**27**	**400**
19–30 y	1,000*	30*	**1,000**	3*	**220**	**27**	**350**
31–50 y	1,000*	30*	**1,000**	3*	**220**	**27**	**360**
Lactation							
14–18 y	1,300*	44*	**1,300**	3*	**290**	**10**	**360**
19–30 y	1,000*	45*	**1,300**	3*	**290**	**9**	**310**
31–50 y	1,000*	45*	**1,300**	3*	**290**	**9**	**320**

NOTE: This table presents Recommended Dietary Allowances (RDAs) in **bold type** and Adequate Intakes (AIs) in ordinary type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover needs of all individuals in the group, but lack of data or uncertainty in the data prevent being able to specify with confidence the percentage of individuals covered by this intake.

Manganese (mg/d)	Molybdenum (µg/d)	Phosphorus (mg/d)	Selenium (µg/d)	Zinc (mg/d)	Potassium (g/d)	Sodium (g/d)	Chloride (g/d)
0.003*	2*	100*	15*	2*	0.4*	0.12*	0.18*
0.6*	3*	275*	20*	**3**	0.7*	0.37*	0.57*
1.2*	**17**	**460**	**20**	**3**	3.0*	1.0*	1.5*
1.5*	**22**	**500**	**30**	**5**	3.8*	1.2*	1.9*
1.9*	**34**	**1,250**	**40**	**8**	4.5*	1.5*	2.3*
2.2*	**43**	**1,250**	**55**	**11**	4.7*	1.5*	2.3*
2.3*	**45**	**700**	**55**	**11**	4.7*	1.5*	2.3*
2.3*	**45**	**700**	**55**	**11**	4.7*	1.5*	2.3*
2.3*	**45**	**700**	**55**	**11**	4.7*	1.3*	2.0*
2.3*	**45**	**700**	**55**	**11**	4.7*	1.2*	1.8*
1.6*	**34**	**1,250**	**40**	**8**	4.5*	1.5*	2.3*
1.6*	**43**	**1,250**	**55**	**9**	4.7*	1.5*	2.3*
1.8*	**45**	**700**	**55**	**8**	4.7*	1.5*	2.3*
1.8*	**45**	**700**	**55**	**8**	4.7*	1.5*	2.3*
1.8*	**45**	**700**	**55**	**8**	4.7*	1.3*	2.0*
1.8*	**45**	**700**	**55**	**8**	4.7*	1.2*	1.8*
2.0*	**50**	**1,250**	**60**	**12**	4.7*	1.5*	2.3*
2.0*	**50**	**700**	**60**	**11**	4.7*	1.5*	2.3*
2.0*	**50**	**700**	**60**	**11**	4.7*	1.5*	2.3*
2.6*	**50**	**1,250**	**70**	**13**	5.1*	1.5*	2.3*
2.6*	**50**	**700**	**70**	**12**	5.1*	1.5*	2.3*
2.6*	**50**	**700**	**70**	**12**	5.1*	1.5*	2.3*

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001); and *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (2005). These reports may be accessed via http://www.nap.edu.

Dietary Reference Intakes (DRIs): Recommended Intakes for Individuals, Total Water and Macronutrients

Food and Nutrition Board, Institute of Medicine, National Academies

Life Stage Group	Total Water[a] (L/d)	Carbohydrate (g/d)	Total Fiber (g/d)	Fat (g/d)	Linoleic Acid (g/d)	α-Linolenic Acid (g/d)	Protein[b] (g/d)
Infants							
0–6 mo	0.7*	60*	ND	31*	4.4*	0.5*	9.1*
7–12 mo	0.8*	95*	ND	30*	4.6*	0.5*	**11.0+**
Children							
1–3 y	1.3*	**130**	19*	ND[c]	7*	0.7*	**13**
4–8 y	1.7*	**130**	25*	ND	10*	0.9*	**19**
Males							
9–13 y	2.4*	**130**	31*	ND	12*	1.2*	**34**
14–18 y	3.3*	**130**	38*	ND	16*	1.6*	**52**
19–30 y	3.7*	**130**	38*	ND	17*	1.6*	**56**
31–50 y	3.7*	**130**	38*	ND	17*	1.6*	**56**
51–70 y	3.7*	**130**	30*	ND	14*	1.6*	**56**
> 70 y	3.7*	**130**	30*	ND	14*	1.6*	**56**
Females							
9–13 y	2.1*	**130**	26*	ND	10*	1.0*	**34**
14–18 y	2.3*	**130**	26*	ND	11*	1.1*	**46**
19–30 y	2.7*	**130**	25*	ND	12*	1.1*	**46**
31–50 y	2.7*	**130**	25*	ND	12*	1.1*	**46**
51–70 y	2.7*	**130**	21*	ND	11*	1.1*	**46**
> 70 y	2.7*	**130**	21*	ND	11*	1.1*	**46**
Pregnancy							
14–18 y	3.0*	**175**	28*	ND	13*	1.4*	**71**
19–30 y	3.0*	**175**	28*	ND	13*	1.4*	**71**
31–50 y	3.0*	**175**	28*	ND	13*	1.4*	**71**
Lactation							
14–18 y	3.8*	**210**	29*	ND	13*	1.3*	**71**
19–30 y	3.8*	**210**	29*	ND	13*	1.3*	**71**
31–50 y	3.8*	**210**	29*	ND	13*	1.3*	**71**

NOTE: This table presents Recommended Dietary Allowances (RDAs) in **bold type** and Adequate Intakes (AIs) in ordinary type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data or uncertainty in the data prevent being able to specify with confidence the percentage of individuals covered by this intake. The plus (+) symbol indicates a change from the prepublication copy due to a calculation error.

[a] *Total* water includes all water contained in food, beverages, and drinking water.

[b] Based on g protein per kg of body weight for the reference body weight, e.g., for adults 0.8 g/kg body weight for the reference body weight.

[c] Not determined.

SOURCES: *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (2002/2005); *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (2005). These reports may be accessed via http://www.nap.edu.

Dietary Reference Intakes (DRIs): Acceptable Macronutrient Distribution Ranges
Food and Nutrition Board, Institute of Medicine, National Academies

	Range (percent of energy)		
Macronutrient	Children, 1–3 y	Children, 4–18 y	Adults
Fat	30–40	25–35	20–35
n-6 Polyunsaturated fatty acids[a] (linoleic acid)	5–10	5–10	5–10
n-3 Polyunsaturated fatty acids[a] (α-linolenic acid)	0.6–1.2	0.6–1.2	0.6–1.2
Carbohydrate	45–65	45–65	45–65
Protein	5–20	10–30	10–35

[a] Approximately 10 percent of the total can come from longer-chain *n*-3 or *n*-6 fatty acids.

SOURCE: *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (2002/2005).

Dietary Reference Intakes (DRIs): Additional Macronutrient Recommendations
Food and Nutrition Board, Institute of Medicine, National Academies

Macronutrient	Recommendation
Dietary cholesterol	As low as possible while consuming a nutritionally adequate diet
Trans fatty acids	As low as possible while consuming a nutritionally adequate diet
Saturated fatty acids	As low as possible while consuming a nutritionally adequate diet
Added sugars	Limit to no more than 25% of total energy

SOURCE: *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (2002/2005).

Dietary Reference Intakes (DRIs): Tolerable Upper Intake Levels (UL[a]), Vitamins
Food and Nutrition Board, Institute of Medicine, National Academies

Life Stage Group	Vitamin A (µg/d)[b]	Vitamin C (mg/d)	Vitamin D (µg/d)	Vitamin E (mg/d)[c,d]	Vitamin K	Thiamin
Infants						
0–6 mo	600	ND[f]	25	ND	ND	ND
7–12 mo	600	ND	25	ND	ND	ND
Children						
1–3 y	600	400	50	200	ND	ND
4–8 y	900	650	50	300	ND	ND
Males, Females						
9–13 y	1,700	1,200	50	600	ND	ND
14–18 y	2,800	1,800	50	800	ND	ND
19–70 y	3,000	2,000	50	1,000	ND	ND
> 70 y	3,000	2,000	50	1,000	ND	ND
Pregnancy						
14–18 y	2,800	1,800	50	800	ND	ND
19–50 y	3,000	2,000	50	1,000	ND	ND
Lactation						
14–18 y	2,800	1,800	50	800	ND	ND
19–50 y	3,000	2,000	50	1,000	ND	ND

[a] UL = The highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantothenic acid, biotin, and carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b] As preformed vitamin A only.

[c] As α-tocopherol; applies to any form of supplemental α-tocopherol.

[d] The ULs for vitamin E, niacin, and folate apply to synthetic forms obtained from supplements, fortified foods, or a combination of the two.

[e] β-Carotene supplements are advised only to serve as a provitamin A source for individuals at risk of vitamin A deficiency.

Riboflavin	Niacin (mg/d)[d]	Vitamin B_6 (mg/d)	Folate (µg/d)[d]	Vitamin B_{12}	Pantothenic Acid	Biotin	Choline (g/d)	Carotenoids[e]
ND	ND	ND	ND	ND	ND	ND	ND	ND
ND	ND	ND	ND	ND	ND	ND	ND	ND
ND	10	30	300	ND	ND	ND	1.0	ND
ND	15	40	400	ND	ND	ND	1.0	ND
ND	20	60	600	ND	ND	ND	2.0	ND
ND	30	80	800	ND	ND	ND	3.0	ND
ND	35	100	1,000	ND	ND	ND	3.5	ND
ND	35	100	1,000	ND	ND	ND	3.5	ND
ND	30	80	800	ND	ND	ND	3.0	ND
ND	35	100	1,000	ND	ND	ND	3.5	ND
ND	30	80	800	ND	ND	ND	3.0	ND
ND	35	100	1,000	ND	ND	ND	3.5	ND

[f] ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); and *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001). These reports may be accessed via http://www.nap.edu.

Dietary Reference Intakes (DRIs): Tolerable Upper Intake Levels (UL[a]), Elements
Food and Nutrition Board, Institute of Medicine, National Academies

Life Stage Group	Arsenic[b]	Boron (mg/d)	Calcium (g/d)	Chromium	Copper (µg/d)	Fluoride (mg/d)	Iodine (µg/d)	Iron (mg/d)	Magnesium (mg/d)[c]
Infants									
0–6 mo	ND[f]	ND	ND	ND	ND	0.7	ND	40	ND
7–12 mo	ND	ND	ND	ND	ND	0.9	ND	40	ND
Children									
1–3 y	ND	3	2.5	ND	1,000	1.3	200	40	65
4–8 y	ND	6	2.5	ND	3,000	2.2	300	40	110
Males, Females									
9–13 y	ND	11	2.5	ND	5,000	10	600	40	350
14–18 y	ND	17	2.5	ND	8,000	10	900	45	350
19–70 y	ND	20	2.5	ND	10,000	10	1,100	45	350
> 70 y	ND	20	2.5	ND	10,000	10	1,100	45	350
Pregnancy									
14–18 y	ND	17	2.5	ND	8,000	10	900	45	350
19–50 y	ND	20	2.5	ND	10,000	10	1,100	45	350
Lactation									
14–18 y	ND	17	2.5	ND	8,000	10	900	45	350
19–50 y	ND	20	2.5	ND	10,000	10	1,100	45	350

[a] UL = The highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for arsenic, chromium, silicon, potassium, and sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b] Although the UL was not determined for arsenic, there is no justification for adding arsenic to food or supplements.

[c] The ULs for magnesium represent intake from a pharmacological agent only and do not include intake from food and water.

[d] Although silicon has not been shown to cause adverse effects in humans, there is no justification for adding silicon to supplements.

[e] Although vanadium in food has not been shown to cause adverse effects in humans,

Manganese (mg/d)	Molybdenum (µg/d)	Nickel (mg/d)	Phosphorus (g/d)	Potassium	Selenium (µg/d)	Silicon[d]	Sulfate	Vanadium (mg/d)[e]	Zinc (mg/d)	Sodium (g/d)	Chloride (g/d)
ND	ND	ND	ND	ND	45	ND	ND	ND	4	ND	ND
ND	ND	ND	ND	ND	60	ND	ND	ND	5	ND	ND
2	300	0.2	3.0	ND	90	ND	ND	ND	7	1.5	2.3
3	600	0.3	3.0	ND	150	ND	ND	ND	12	1.9	2.9
6	1,100	0.6	4.0	ND	280	ND	ND	ND	23	2.2	3.4
9	1,700	1.0	4.0	ND	400	ND	ND	ND	34	2.3	3.6
11	2,000	1.0	4.0	ND	400	ND	ND	1.8	40	2.3	3.6
11	2,000	1.0	3.0	ND	400	ND	ND	1.8	40	2.3	3.6
9	1,700	1.0	3.5	ND	400	ND	ND	ND	34	2.3	3.6
11	2,000	1.0	3.5	ND	400	ND	ND	ND	40	2.3	3.6
9	1,700	1.0	4.0	ND	400	ND	ND	ND	34	2.3	3.6
11	2,000	1.0	4.0	ND	400	ND	ND	ND	40	2.3	3.6

there is no justification for adding vanadium to food and vanadium supplements should be used with caution. The UL is based on adverse effects in laboratory animals and this data could be used to set a UL for adults but not children and adolescents.

f ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001); *and Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (2005). These reports may be accessed via http://www.nap.edu.

Dietary Reference Intakes (DRIs): Estimated Average Requirements for Groups
Food and Nutrition Board, Institute of Medicine, National Academies

Life Stage Group	CHO (g/d)	Protein (g/kg/d)	Vit A (μg/d)[a]	Vit C (mg/d)	Vit E (mg/d)[b]	Thiamin (mg/d)	Ribo-flavin (mg/d)	Niacin (mg/d)[c]	Vit B_6 (mg/d)
Infants									
7–12 mo		1.0							
Children									
1–3 y	100	0.87	210	13	5	0.4	0.4	5	0.4
4–8 y	100	0.76	275	22	6	0.5	0.5	6	0.5
Males									
9–13 y	100	0.76	445	39	9	0.7	0.8	9	0.8
14–18 y	100	0.73	630	63	12	1.0	1.1	12	1.1
19–30 y	100	0.66	625	75	12	1.0	1.1	12	1.1
31–50 y	100	0.66	625	75	12	1.0	1.1	12	1.1
51–70 y	100	0.66	625	75	12	1.0	1.1	12	1.4
> 70 y	100	0.66	625	75	12	1.0	1.1	12	1.4
Females									
9–13 y	100	0.76	420	39	9	0.7	0.8	9	0.8
14–18 y	100	0.71	485	56	12	0.9	0.9	11	1.0
19–30 y	100	0.66	500	60	12	0.9	0.9	11	1.1
31–50 y	100	0.66	500	60	12	0.9	0.9	11	1.1
51–70 y	100	0.66	500	60	12	0.9	0.9	11	1.3
> 70 y	100	0.66	500	60	12	0.9	0.9	11	1.3
Pregnancy									
14–18 y	135	0.88	530	66	12	1.2	1.2	14	1.6
19–30 y	135	0.88	550	70	12	1.2	1.2	14	1.6
31–50 y	135	0.88	550	70	12	1.2	1.2	14	1.6
Lactation									
14–18 y	160	1.05	885	96	16	1.2	1.3	13	1.7
19–30 y	160	1.05	900	100	16	1.2	1.3	13	1.7
31–50 y	160	1.05	900	100	16	1.2	1.3	13	1.7

NOTE: This table presents Estimated Average Requirements (EARs), which serve two purposes: for assessing adequacy of population intakes and as the basis for calculating Recommended Dietary Allowances (RDAs) for individuals. EARs have not been established for vitamin D, vitamin K, pantothenic acid, biotin, choline, calcium, chromium, fluoride, manganese, or other nutrients not yet evaluated via the DRI process.

[a] As retinol activity equivalents (RAEs). 1 RAE = 1 μg retinol, 12 μg β-carotene, 24 μg α-carotene, or 24 μg β-cryptoxanthin. The RAE for dietary provitamin A carotenoids is twofold greater than retinol equivalents (RE), whereas the RAE for preformed vitamin A is the same as RE.

[b] As α-tocopherol. α-Tocopherol includes *RRR*-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the *2R*-stereoisomeric forms of α-tocopherol (*RRR*-, *RSR*-, *RRS*-, and *RSS*-α-tocopherol) that occur in fortified foods and supplements. It does not include the *2S*-stereoisomeric forms of α-tocopherol (*SRR*-, *SSR*-, *SRS*-, and *SSS*-α-tocopherol), also found in fortified foods and supplements.

Folate (μg/d)[a]	Vit B_{12} (μg/d)	Copper (μg/d)	Iodine (μg/d)	Iron (mg/d)	Magnesium (mg/d)	Molybdenum (μg/d)	Phosphorus (mg/d)	Selenium (μg/d)	Zinc (mg/d)
				6.9					2.5
120	0.7	260	65	3.0	65	13	380	17	2.5
160	1.0	340	65	4.1	110	17	405	23	4.0
250	1.5	540	73	5.9	200	26	1,055	35	7.0
330	2.0	685	95	7.7	340	33	1,055	45	8.5
320	2.0	700	95	6	330	34	580	45	9.4
320	2.0	700	95	6	350	34	580	45	9.4
320	2.0	700	95	6	350	34	580	45	9.4
320	2.0	700	95	6	350	34	580	45	9.4
250	1.5	540	73	5.7	200	26	1,055	35	7.0
330	2.0	685	95	7.9	300	33	1,055	45	7.3
320	2.0	700	95	8.1	255	34	580	45	6.8
320	2.0	700	95	8.1	265	34	580	45	6.8
320	2.0	700	95	5	265	34	580	45	6.8
320	2.0	700	95	5	265	34	580	45	6.8
520	2.2	785	160	23	335	40	1,055	49	10.5
520	2.2	800	160	22	290	40	580	49	9.5
520	2.2	800	160	22	300	40	580	49	9.5
450	2.4	985	209	7	300	35	1,055	59	10.9
450	2.4	1,000	209	6.5	255	36	580	59	10.4
450	2.4	1,000	209	6.5	265	36	580	59	10.4

[c] As niacin equivalents (NE). 1 mg of niacin = 60 mg of tryptophan.

[d] As dietary folate equivalents (DFE). 1 DFE = 1 μg food folate = 0.6 μg of folic acid from fortified food or as a supplement consumed with food = 0.5 μg of a supplement taken on an empty stomach.

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001), and *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (2002/2005). These reports may be accessed via www.nap.edu.